Medicinrådet

Bilag til Medicinrådets anbefaling (revurdering) vedrørende esketamin til behandling af behandlingsresistent depression

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. esketamin, version 2.0
2. Forhandlingsnotat fra Amgros vedr. esketamin
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog
4. Medicinrådets vurdering vedr. esketamin til behandling af esketamin, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. esketamin til behandling af esketamin, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Esketamin

Behandlingsresistent depression hos voksne

Version 2.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

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1. Begreber og forkortelser

AIP:	Apotekernes indkøbspris
AUP:	Apotekernes udsalgspris
DKK:	Danske kroner
DRG:	Diagnose Relaterede Grupper
MADRS:	Montgomery & Åsberg Depression Rating Scale
MDD:	Major Depressive Disorder
MDE:	Major Depressive Episode
MSM:	Maudsley Staging Method
OAD:	Orale antidepressiver
SAIP:	Sygehusapotekernes indkøbspris
TRIDEN:	Treatment Resistant Depression in Denmark

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for esketamin, sammenlignet med komparator, ca. [redacted] DKK pr. patient for patienter med behandlingsresistent depression. For patienter med moderat til svær behandlingsresistent depression og MSM ≥ 9 er de inkrementelle omkostninger ca. [redacted] DKK. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 72.000 DKK og 81.000 DKK pr. patient. De inkrementelle omkostninger ved behandling med esketamin er i høj grad drevet af lægemiddelomkostningerne.

Der er flere betydningsfulde usikkerheder i modellen, som har betydning for analysens resultat. Disse bliver i analysen belyst ved følsomhedsanalyser. Her vises det, at usikkerhederne vedr. behandlingslængde for esketamin, dosering af esketamin og generelle sygdomsomkostninger ved behandlingsresistent depression har betydning for niveauet af inkrementelle omkostninger ved en anbefaling af esketamin. Yderligere er der usikkerhed omkring omkostning ved genbehandling med esketamin, såfremt patienter oplever et tilbagefald efter at have haft gavn af behandling tidligere. Samtidig forventes der at være en stigning i omkostninger til lokaler på ambulatorierne ved at indføre esketamin som mulig standardbehandling. Disse omkostninger bliver ikke adresseret i den anvendte model.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af esketamin som mulig standardbehandling vil være ca. [redacted] DKK og ca. [redacted] DKK i det femte år efter en anbefaling for hhv. den fulde patientpopulation og subpopulationen med MSM ≥ 9. Når analysen er udført med AIP, er budgetkonsekvenserne hhv. ca. 116 mio. og 81 mio. DKK i det femte år.

3. Introduktion

Esketamin blev i august 2020 vurderet af Medicinrådet til behandling af patienter, der lider af behandlingsresistent depression[1]. Revurderingen er udarbejdet, fordi Medicinrådet 18. december 2020 modtog en anmodning om at revurdere den tidligere anbefaling af esketamin på baggrund af, at der er kommet nye opdaterede data på sikkerhed og den vedvarende effekt. Revurderingen indeholder to kliniske spørgsmål, hvor klinisk spørgsmål 1 er identisk med den foregående vurdering, mens klinisk spørgsmål 2 er nyt og vedrører en subgruppe med mere svær grad af sygdom, hvor sværhedsgraden af den depressive episode er defineret som patienter med *Maudsley Staging Method* (MSM) ≥ 9.

Formålet med den sundhedsøkonomiske analyse er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for

regionerne ved anbefaling af esketamin som mulig standardbehandling på danske hospitaler til behandlingsresistent depression.

Den sundhedsøkonomiske model i genansøgningen er baseret på den samme data, som dannede udgangspunktet for den oprindelige ansøgning, men indeholder nye analyser af MSM $\geq$ 9 subpopulation. Ligeledes er strukturen i den sundhedsøkonomiske model uændret.

3.1 Patientpopulation

Depression inddeles i mild, moderat og svær depression. Nogle patienter responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende. Ifølge Sundhedsstyrelsen omfatter behandlingsresistent depression voksne patienter over 18 år (både ambulante og indlagte) med moderat til svær depression, diagnosticeret efter ICD-10 (WHO's diagnoseliste) kriterier eller vurderet behandlingsresistent på Rating Scale for Treatment-Resistant Depression, f.eks. Maudsley Staging Method (MSM)[2,3].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af esketamin på baggrund af nedenstående kliniske spørgsmål. Klinisk spørgsmål 1 indgik også i den oprindelige ansøgning, mens klinisk spørgsmål 2 er tilføjet på baggrund af de nye analyser, ansøger har udarbejdet i forbindelse med genansøgningen.

Klinisk spørgsmål 1:

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

Klinisk spørgsmål 2:

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med moderat til svær behandlingsresistent depression vurderet ud fra MSM (MSM $\geq$ 9) i den aktuelle moderate til svære depressive episode?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for esketamin sammenlignet med orale antidepressiver (OAD). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med esketamin er, som i den oprindelige vurdering, lavet på baggrund af data fra studierne TRANSFORM-1, 2 og 3[4–6] samt SUSTAIN-1[7]. TRANSFORM studierne var alle multicenter dobbeltblindede, parallelgrupperede, randomiserede fase-3 studier. Studierne havde til formål at evaluere effekten, sikkerheden og tolerancen af intranasal esketamin + nyt OAD overfor behandling med intranasal placebo + nyt OAD hos patienter med *behandlingsresistent depression*. I TRANSFORM-1 blev der givet en af to faste doser af esketamin to gange ugentligt, mens der i TRANSFORM-2 blev givet fleksible doser (56 mg eller 84 mg). I begge studier var patienter 18-64 år. I TRANSFORM-3 blev der givet én af tre fleksible doser (28 mg, 56 mg, eller 84 mg), og patienterne var 64 år eller ældre. I alle tre studier blev resultaterne opgjort efter 4 ugers induktionsfase, og det primære endepunkt var ændring i *Montgomery & Åsberg Depression Rating Scale* (MADRS) totalscore, målt fra baseline i induktionsfasen til uge 4 (dag 28) eller sidste måling i induktionsfasen.

SUSTAIN-1 var et internationalt multicenter, dobbeltblindet, randomiseret relaps fase-3 studie. Studiet sammenligner effekt, sikkerheden og tolerancen af fortsat intranasal esketaminbehandling (fleksibel dosering) + OAD med ophør af intranasal esketamin-behandling (overgår til intranasal placebo + OAD) hos patienter, der har opretholdt *response* med intranasal esketaminbehandling gennem induktionsfasen (4 uger) og optimeringsfasen (12 uger). Efter induktions- og optimeringsfasen blev patienterne, der havde opnået *response* eller *remission,* randomiseret til i vedligeholdelsesfasen at fortsætte med esketamin + OAD eller placebo + OAD. Varigheden af denne fase var individuel (median mellem 10 og 19 uger) og afhang af, hvornår patienten indtrådte i studiet, og hvornår et relaps opstod. Fasen forløb, indtil et tilstrækkeligt antal patienter havde oplevet tilbagefald baseret på statistiske styrkeberegninger. Det primære endepunkt for SUSTAIN-1 var tid til tilbagefald for patienter i stabil *remission* efter behandling med esketamin i tidligere faser.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en Markov-model til at estimere omkostningerne forbundet med behandlingen med esketamin. Modellen består af en række sygdomsstadier, som patienten kan befinde sig i på et givet tidspunkt (se Figur 1), hvor sygdomsrelaterede omkostninger estimeres ud fra det sygdomsstadie, som patienten befinder sig i.

Patienten kan i modellen være i stadierne *Major Depressive Episode* (MDE), *Response, Remission* eller Recovery afhængig af deres tilstand. Modellen benytter en cykluslængde på 4 uger.

Den initiale cyklus i modellen defineres som akutfasen, hvor patienten befinder sig i stadiet *MDE*. Efter første cyklus kan patienten opnå enten *remission* eller *response*. Såfremt patienten ikke opnår *response* eller *remission*, forbliver patienten i MDE-stadiet og overgår til *Subsequent treatment*. *Response* defineres i modellen som ≥ 50 % forbedring fra baseline på (MADRS)-scoren. *Remission* er defineret ved MADRS-score ≤ 12. Sandsynlighed for at opnå *response* eller *remission* i akutfasen er i ansøgers model baseret på TRANSFORM-2 for begge behandlingsarme, og separate sandsynligheder er estimeret for hhv. den fulde population og MSM ≥ 9 populationen.

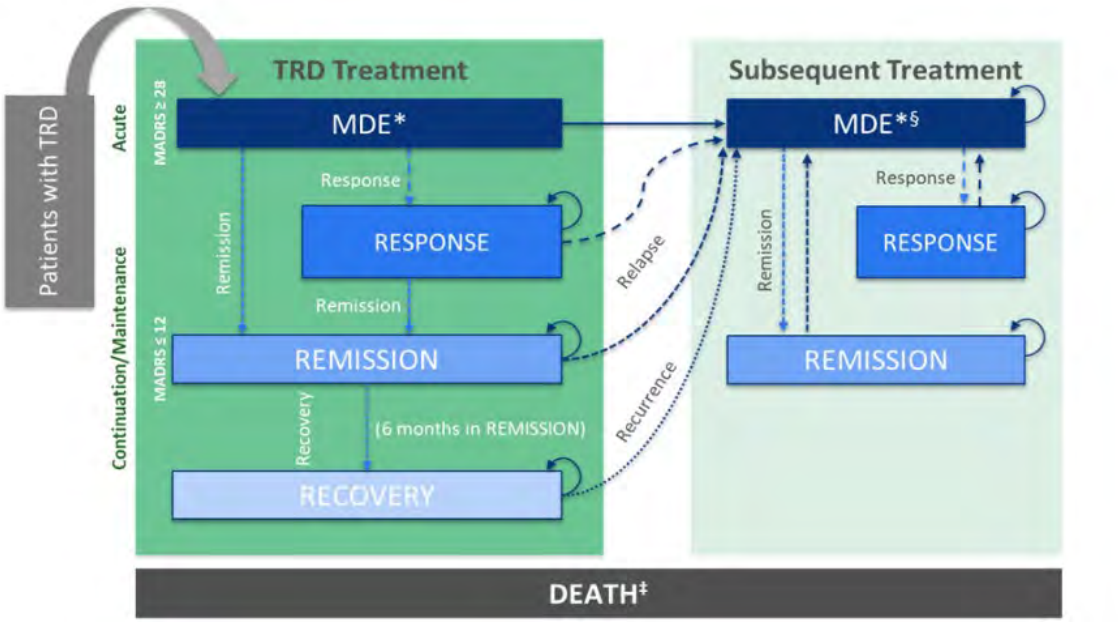
Efter akutfasen indledes optimerings-/vedligeholdelsesfasen, som dækker over modellens resterende cyklusser, baseret på SUSTAIN-1. Patienterne, der opnåede *response* eller *remission* efter akutfasen, har i hver cyklus en risiko for at opleve et *relapse* (tilbagefald), karakteriseret ved at patienten bevæger sig tilbage til stadiet *MDE* med efterfølgende behandling (*Subsequent treatment).* Patienterne i *response*-stadiet har ligeledes en sandsynlighed i hver cyklus for at bevæge sig til *remission*. Såfremt en patient har været i *remission* i 36 uger, overgår de automatisk til stadiet *Recovery*. Ansøger antager her, at 70 % stopper behandling med esketamin, når de bevæger sig til dette stadie. Yderligere antages det, at 99,9 % vil være stoppet med esketaminbehandling efter 2 år, uanset hvilket stadie de befinder sig i på pågældende tidspunkt. Modellen, ansøger har sendt ind som hovedanalyse, tager ikke højde for genbehandling med esketamin ved tilbagefald af depressionen.

I *Recovery*-stadiet har patienten ligeledes en risiko for at få et tilbagefald, som medfører, at patienten bevæger sig tilbage til stadiet *MDE*, hvor de modtager *subsequent treatment* (denne transition benævnes som *recurrence* i modellen). Estimeringen af risici for *relapse* og *recurrence* baseres på data fra SUSTAIN-1 for begge behandlingsarme, hvor separate sandsynligheder er blevet estimeret for hhv. den fulde population og MSM ≥ 9 populationen.

Når patienten overgår til efterfølgende behandling, kan patienten ligeledes opnå *response* og *remission* samt opleve tilbagefald i form af ny *Major Depressive Episode,* men står her overfor andre transitionssandsynligheder. Til at estimere disse sandsynligheder har ansøger taget udgangspunkt i data fra en sundhedsøkonomisk evaluering, foretaget af *National Health Services (NHS)*, hvor omkostningseffektiviteten af lithium og atypiske antipsykotikaer til behandlingsresistent depression undersøges[8].

I hvert stadie af modellen har patienten en risiko for at dø. Denne risiko er baseret på data for generel dødelighed i befolkningen samt data på risiko for selvmord hos patienter med behandlingsresistent depression. For sidstnævnte benyttes estimater fra en publiceret metaanalyse[9].

Figur 2. Modelstruktur af den sundhedsøkonomiske analyse



*Massiv depressiv episode

Medicinrådets vurdering af ansøgers model

Sekretariatet har i vurderingsrapporten vurderet effekten af esketamin + OAD ud fra studierne TRANSFORM-1, TRANSFORM-2, TRANSFORM-3 og SUSTAIN-1. I den kliniske del vurderes akutfasen ud fra de tre TRANSFORM-studier. Ansøger har argumenteret for, at TRANSFORM-1 ikke afspejler klinisk praksis, og at TRANSFORM-3 er baseret på ældre (> 65 år) patienter. Ansøger vælger derfor i den sundhedsøkonomiske model, at akutfasen tager udgangspunkt i TRANSFORM-2, som inkluderer patienter fra 18 til 64 år.

I Medicinrådets sundhedsøkonomiske analyse er der i den akutte fase i stedet for taget udgangspunkt i poolede resultater fra både TRANSFORM-1, 2 og 3. Dette er valgt for at sikre overensstemmelse mellem den kliniske vurdering og den sundhedsøkonomiske analyse. Medicinrådet præsenterer en følsomhedsanalyse, hvor data fra TRANSFORM2 benyttes. Transitionssandsynlighederne, som Medicinrådet anvender i sin hovedanalyse, kan findes i Tabel 1 og Tabel 2. Fordelingen af patienter i modellens stadier over tid på tværs af populationer og behandling kan ses i, Figur 4, Figur 5 og Figur 6.

Fagudvalget vurderer, at hvis esketamin + OAD har haft effekt på en patient, og patienten får et tilbagefald, ville det klinisk give mening at forsøge at genbehandle med esketamin. Ansøgers hovedanalyse tager ikke højde for genbehandling, men ansøger indsendte på opfordring fra Medicinrådet en alternativ model hvor mulighed for genbehandling var inkluderet. Medicinrådet vurderer at denne model ikke var mere passende at anvende, som følge af manglen på data vedrørende effekt af genbehandling med esketamin. Dette var i overensstemmelse med ansøgers vurdering. Resultatet af Medicinrådets hovedanalyse bør derfor ses i lyset af dette.

Varigheden af esketaminbehandlingen er endnu uafklaret. Produktresuméet for esketamin anbefaler, at behandling af patienter, der oplever forbedring af deres depressive symptomer indenfor 4 uger, fortsætter deres behandling i minimum 6 måneder. Under vedligeholdelsesfasen skal doseringen af esketamin individualiseres til den laveste hyppighed, der kan opretholde *remission*/*response*. Behovet for fortsat behandling skal jævnligt revurderes. Fagudvalget vurderer, at den egentlige behandlingslængde ikke kan estimeres ud fra foreliggende datagrundlag, men at den formentlig er længere end de 9 måneder, som ansøger antager i hovedanalysen. Det vurderes samtidig af fagudvalget, at man i praksis nok vil behandle patienter med MSM ≥ 9 længere tid end den fulde patientpopulation, såfremt man opnår den ønskede effekt. Det vurderes derfor, at omkring 50 % af patienterne med MSM ≥ 9 vil fortsætte med behandling efter at have nået stadiet *recovery,* og at 50 % fortsat vil være i behandling efter 2 år. Som følge af den usikkerhed der er forbundet med behandlingslængde af esketamin, præsenterer Medicinrådet en række følsomhedsanalyser, hvor denne behandlingslængde varieres for begge patientpopulationer.

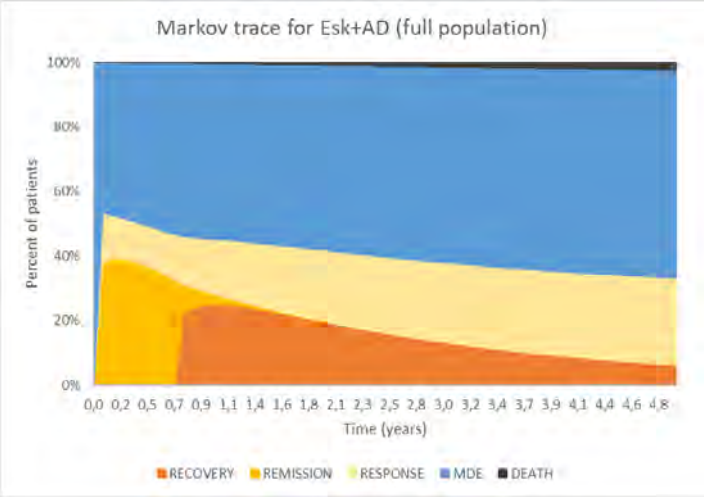
Tabel 1. Sandsynlighed for bevægelse mellem de forskellige stadier i Medicinrådets analyse for den fulde patientpopulation, baseret på TRANSFORM-1, 2, 3 og SUSTAIN-1 (klinisk spørgsmål 1)

Behandling	MDE til *remission*	MDE til *response*	*Response* til *remission*	Relaps	Tab af *response*	Tilbagefald
Esketamin	0,381	0,153	0,199	0,056	0,042	0,029
Placebo	0,254	0,127	0,124	0,123	0,149	0,029

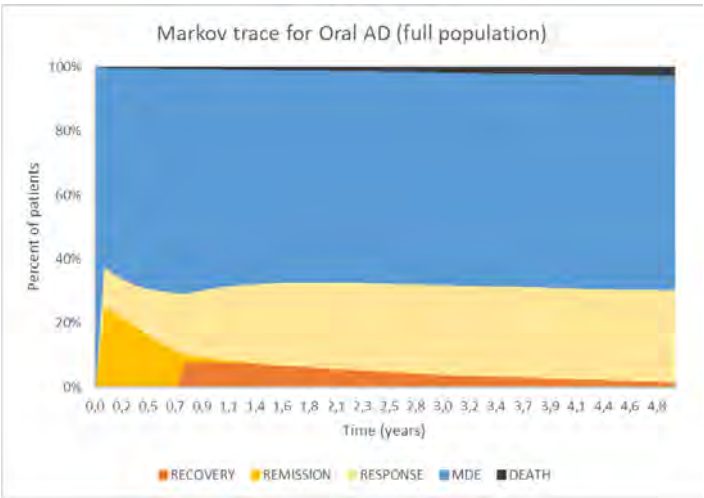
Tabel 2. Sandsynlighed for bevægelse mellem de forskellige stadier i Medicinrådets analyse for MSM ≥ 9 populationen baseret på TRANSFORM-1, 2, 3 og SUSTAIN-1 (klinisk spørgsmål 2)

Behandling	MDE til *remission*	MDE til *response*	*Response* til *remission*	Relaps	Tab af *response*	Tilbagefald
Esketamin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

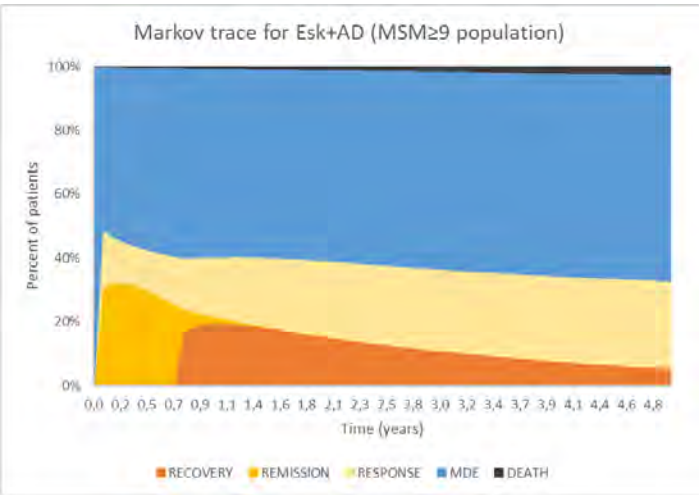
Figur 3. Fordeling af patienter i modellens stadier over tid ved behandling med esketamin + OAD for den fulde patientpopulation (klinisk spørgsmål 1)



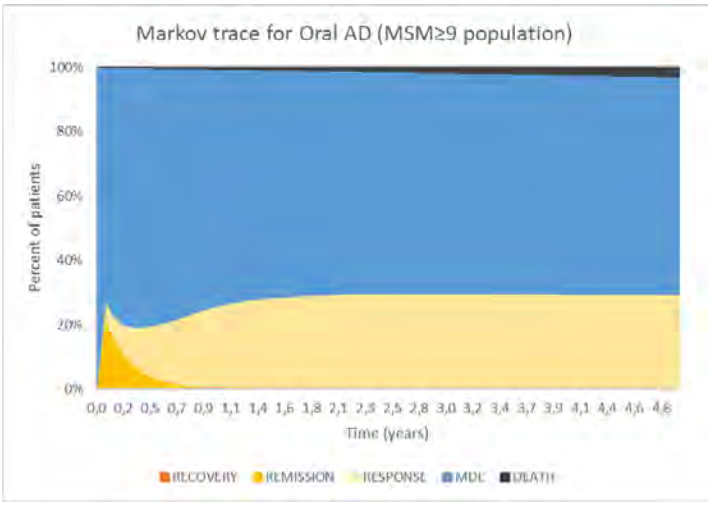
Figur 4. Fordeling af patienter i modellens stadier over tid ved behandling med OAD af den fulde patientpopulation (klinisk spørgsmål 1)



Figur 5. Fordeling af patienter i modellens stadier over tid ved behandling med esketamin + OAD af MSM ≥ 9 populationen (klinisk spørgsmål 2)



Figur 6. Fordeling af patienter i modellens stadier over tid ved behandling med OAD af MSM ≥ 9 populationen (klinisk spørgsmål 2)



Medicinrådet vurderer, at der er usikkerhed omkring effekten af behandling med esketamin i vedligeholdelsesfasen, siden SUSTAIN-1 kun inkluderede patienter, der tidligere var blevet behandlet med og havde haft effekt af esketamin. Det var kun disse patienter, som blev randomiseret i studiet til at fortsætte behandling med esketamin + OAD eller placebo + OAD. Som følge af denne usikkerhed præsenteres en følsomhedsanalyse, hvor sandsynligheden for *relapse* og *recurrence* bliver sat lig hinanden for esketamin + OAD og placebo + OAD.

Medicinrådet vurderer, at datagrundlaget for transitionssandsynlighederne hos MSM ≥ 9 populationen er ret lille. Der præsenteres derfor også en følsomhedsanalyse, hvor transitionssandsynlighederne for den fulde patientpopulation benyttes for MSM ≥ 9 populationen.

Medicinrådet accepterer, at publikationen fra *NHS* anvendes til at estimere transitionssandsynlighederne, når patienterne modtager efterfølgende behandling. Det bemærkes dog, at ansøger har estimeret sandsynligheden for at opnå respons eller remission ved efterfølgende behandling, baseret på data for patienter der ikke har opnået nogen effekt af den efterfølgende behandling efter 4 uger. Medicinrådet vurderer, at man bør tage udgangspunkt i både de patienter, der opnår respons/remission efter 4 uger, og dem som ikke gør. Der udregnes derfor en ny transitionssandsynlighed i Medicinrådets hovedanalyse, baseret på en vægtning af disse to patientgrupper. Transitionssandsynlighederne, benyttet i modellen for efterfølgende behandling, kan findes i Tabel 3.

Tabel 3. Sandsynlighed for bevægelse mellem de forskellige stadier ved efterfølgende behandling i Medicinrådets analyse (gældende for den fulde patientpopulation samt MSM ≥ 9 populationen)

Behandling	*Response*	*Remission*	Relaps	Tab af *response*
OAD (efterfølgende behandling)	0,045	0,070	0,042	0,104

Medicinrådet accepterer ikke ansøgers valg om kun at inkludere TRANSFORM-2 studiet til at estimere effekt af behandling i den akutte fase. Da den kliniske vurdering er baseret på en metaanalyse af de tre TRANSFORM studier, anvendes også disse i en sundhedsøkonomisk model. Sekretariatet anvender derfor poolede data fra TRANSFORM-1, -2 og -3 i hovedanalysen, men udarbejder en følsomhedsanalyse med data fra TRANSFORM-2 alene.

For MSM ≥ 9 populationen ændrer Medicinrådet andelen, der stopper behandling med esketamin ved recovery fra 70 % til 50 %. Ligeledes ændres andelen, der er stopper behandling efter 2 år fra 99,9 % til 50 %.

Sandsynligheden for at opnå remission og response på efterfølgende behandling kommer i Medicinrådets hovedanalyse til at tage udgangspunkt i både patienter, der opnår response efter 4 ugers behandling, og dem som ikke gør det. De anvendte sandsynligheder stammer fra samme NHS-publikation, som ansøger benytter.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 5 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Siden modellen ikke tager højde for genbehandling med esketamin jf. afsnit 4.1.1, accepterer Medicinrådets ansøgers valgte tidshorisont.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af behandling med esketamin + OAD sammenlignet med OAD. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger. Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i et givet stadie.

4.2.1 Lægemiddelomkostninger

Den anbefalede dosis af esketamin er 56 mg eller 84 mg hver uge eller hver anden uge.

Ansøger anvender den gennemsnitlige doseringsfrekvens og dosis fra TRANSFORM-2 (i akutfasen) og SUSTAIN-1 (i optimeringsfasen og vedligeholdelsesfasen). Frekvens og dosis er opgjort separat for den fulde patientpopulation og MSM ≥ 9 populationen. Se Tabel 4 og Tabel 5 for gennemsnitlige antal sessioner (frekvens) og antal enheder (dosis).

Tabel 4. Gennemsnitlig dosis og frekvens for esketamin pr. uge for den fulde patientpopulation (klinisk spørgsmål 1)

Akutfase		Vedligeholdelsesfase (uge 5-8)		Vedligeholdelsesfase (uge 9-40)		Recovery	
Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge
1,85	2,53	0,99	2,60	0,71	2,60	0,67	2,56

Tabel 5. Gennemsnitlig dosis og frekvens for esketamin pr. uge for MSM ≥ 9 population (klinisk spørgsmål 2)

Akutfase		Vedligeholdelsesfase (uge 5-8)		Vedligeholdelsesfase (uge 9-40)		Recovery	
Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge	Frekvens pr. uge	Dosis pr. uge
1,92	2,64	1	2,72	0,73	2,72	0,62	2,67

Ansøger anvender upubliceret *Real World Evidence*-data, som er baseret på en registerundersøgelse, offentliggjort i rapporten (TRIDEN: Treatment Resistant Depression in Denmark) til at afgøre, hvilke OAD-patienter der er i behandling med hhv. SSRI- og SNRI-lægemidler. Lægemidlerne anvendes til gruppen, der ikke modtager esketamin og som add-on til esketamingruppen. De anvendte SSRI og SNRI er i overensstemmelse med anbefalinger i dansk klinisk praksis. De fire lægemidler, to SSRI-produkter (escitalopram og sertralin) og to SNRI-produkter (duloxetin og venlafaxin) anvendes i samme grad og udgør således hver 25 % af forbruget i begge behandlingsarme og i begge patient-populationer, se Tabel 6.

Tabel 6. Dosis pr. dag for anvendte SSRI- og SNRI-præparater

Lægemiddel	Dosis pr. dag	Fordeling
Duloxetin	120 mg	25%
Escitalopram	20 mg	25%
Sertralin	200 mg	25%
Venlafaxin	375 mg	25%

Lægemiddelprisen for esketamin er i SAIP, mens de resterende lægemidler er i AUP, da disse distribueres via primærsektoren, se Tabel 7.

Tabel 7. Anvendte lægemiddelpriser SAIP/AUP (november 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Esketamin	28 mg	1 stk.	[redacted]	Amgros
Duloxetin	60 mg	98 stk.	57,95	Medicinpriser.dk
Escitalopram	20 mg	100 stk.	44,6	
Sertralin	50 mg	100 stk.	27,65	
Venlafaxin	75 mg	100 stk.	43,15	

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Da esketamin både kan gives som 28 mg, 56 mg eller 84 mg, og enten én gang om ugen eller hver anden uge, er der stor usikkerhed om, hvad gennemsnitlig dosis- og doseringshyppighed vil være i dansk klinisk praksis. Da patienter i SUSTAIN-1 er selekterede patienter, kunne dosis og frekvens være højere i dansk klinisk praksis.

Medicinrådet udarbejder derfor følsomhedsanalyser, der belyser hhv. lav dosis og høj dosis hhv. én gang om ugen og hver anden uge.

Medicinrådet accepterer ansøgers antagelser for lægemiddelomkostninger til hovedanalysen.

4.2.2 Hospitalsomkostninger

Sygdomsrelaterede omkostninger

Til at estimere ressourceomkostninger, der relaterer sig til generel behandling for begge populationer på tværs af stadier anvender ansøger den førnævnte rapport TRIDEN. Data er fra Landspatientregisteret i perioden 1996 til 2016, hvor behandling af patienter med behandlingsresistent depression belyses. Rapporten indeholder en opgørelse af antal lægebesøg, konsultation hos psykiater, psykolog, hospitalsdage, akutmodtagelse og primære sundhedsspecialister. Som følge af forskelle i sværhedsgrad af sygdom, estimeres der separate sygdomsrelaterede omkostninger for den fulde patientpopulation og MSM ≥ 9 populationen.

Sygdomsrelaterede omkostninger for den fulde patientpopulation (klinisk spørgsmål 1)
Til af estimere sygdomsrelaterede omkostninger for den fulde patientpopulation i MDE-stadiet, anvender ansøger det gennemsnitlige forbrug observeret i TRIDEN for patienter, der behandles med SSRI eller SNRI som 1. linjebehandling, se Tabel 8. Se Tabel 9 for enhedsomkostninger til ressourcerne og Tabel 10 for samlede omkostninger til MDE-stadiet. For at finde omkostningerne til stadierne *remission* og *recovery* i den fulde patientpopulation anvender ansøger et svensk registerstudie, der opgør det proportionelle forhold i omkostninger mellem MDE-stadiet og *remission*[10]. For stadiet *response* antager ansøger et gennemsnit af MDE- og *remission*sstadiet. De udregnede omkostninger for disse stadier kan findes i Tabel 11.

Tabel 8. Gennemsnitlig antal besøg/hospitalsdage pr. år for behandlingsresistent depression for MDE-stadiet hos den fulde patientpopulation (klinisk spørgsmål 1)

Ressource	SSRI	SNRI
Psykiatriske kontakter		
Akut hospitalsindlæggelse	4,7	5,3
Elektiv hospitalsindlæggelse	1,0	1,1
Akut ambulant besøg	0,2	0,2
Somatiske kontakter		
Akut hospitalsindlæggelse	2,6	2,0
Elektiv hospitalsindlæggelse	0,7	0,6

Ressource	SSRI	SNRI
Akut ambulant besøg	0,4	0,3
Ambulant besøg	3,2	3,0
Lægebesøg	9,2	9,6

Tabel 9. Enhedsomkostninger pr. ressource benyttet for den fulde patientpopulation (klinisk spørgsmål 1)

Administration	Enhedsomkostning [DKK]	Kilde
Psykiatrisk ambulant besøg	1.944	DRG-psykiatritakst 2021
Somatisk ambulant besøg	2.116	19MA98
Akut ambulant psykiatrisk besøg	1.944	DRG-2020
Akut ambulant somatisk besøg	2.116	19MA98
Hospitalsindlæggelse psykiatri	3.885	DRG-psykiatritakst 2021
Hospitalsindlæggelse somatisk	16.487	19MA02
Hjemmebesøg	2.116	19MA98
Psykiatrisk hjemmebesøg	1.944	DRG-psykiatritakst 2021
Lægebesøg	146,79	Medicinrådets værdisætning af enhedsomkostninger

Tabel 10. Estimater på ressourceomkostninger pr. patient i MDE-stadiet hos den fulde patientpopulation (klinisk spørgsmål 1)

Ressource	MDE-omkostninger [DKK]
Psykiatriske kontakter	
Akut hospitalsindlæggelse	19.425
Elektiv hospitalsindlæggelse	4.079

Ressource	MDE-omkostninger [DKK]
Akut ambulant besøg	389
Somatiske kontakter	
Akut hospitalsindlæggelse	16.487
Elektiv hospitalsindlæggelse	10.717
Akut ambulant besøg	741
Ambulant besøg	6.560
Lægebesøg	1.380
Total årlige omkostninger	59.777
Omkostninger pr. cyklus	4.582

Tabel 11: Omkostninger pr. cyklus og pr. sygdomsstadie hos den fulde patientpopulation (klinisk spørgsmål 1)

Sundhedsstadie	Omkostninger pr. cyklus [DKK]	Kilde
MDE	4.582	TRIDEN, DRG
Response	2.614	TRIDEN, DRG, Ekman et al. [10]
Remission	646	TRIDEN, DRG, Ekman et al. [10]
Recovery	646	TRIDEN, DRG, Ekman et al. [10]

Sygdomsrelaterede omkostninger for MSM ≥ 9 populationen (klinisk spørgsmål 2)
Omkostninger for MSM ≥ 9 populationen er i MDE-stadiet baseret på den gennemsnitlige omkostning fundet i TRIDEN for patienter med en svær depressiv episode, der modtog behandling med SSRI eller SNRI. Ansøger har ikke i yderligere detaljer beskrevet metoden, hvorpå den gennemsnitlige omkostning er beregnet. På tilsvarende måde, som for hele populationen, udregnes omkostninger til *remission* og *recovery* på basis af

studiet, der opgør proportionelle forhold i omkostninger mellem MDE-stadiet og *remission*. *Response* udregnes igen som et gennemsnit af MDE- og *remissions*stadiet.

Tabel 12: Omkostninger pr. cyklus og pr. sygdomsstadie for MSM ≥ 9 populationen (klinisk spørgsmål 2)

	MDE [DKK]	*Response* [DKK]	*Remission* [DKK]	Recovery [DKK]
Psykiatriske kontakter	57.529			
Somatiske kontakter	15.129			
Praktiserende Læge	1.100			
Samlet årlig omkostning	**73.758**	**42.079**	**10.401**	**10.401**
Samlet omkostning pr. cyklus	**5.654**	**3.226**	**797**	**797**

Medicinrådets vurdering af ansøgers antagelser vedr. sygdomsrelaterede omkostninger

Medicinrådet accepterer ansøgers antagelser vedr. sygdomsrelaterede omkostninger.

Administrations- og monitoreringsomkostninger

Ansøger antager, at administrationsomkostning pr. behandling er identisk mellem de to patientpopulationer, beskrevet i klinisk spørgsmål 1 og 2.

Administration af esketamin og den efterfølgende observation skal overvåges af sundhedspersonale. Ansøger antager, at en sundhedsfaglig person kan håndtere 3 patienter samtidig. Administrationen af esketamin forventer ansøger vil blive varetaget af en reservelæge, mens observationen efter dosering forventes at blive varetaget af en sygeplejerske. Til at estimere omkostningen forbundet med dette har ansøger taget udgangspunkt i Medicinrådets enhedsomkostninger[11]. Ansøger antager, at der er 5 minutters pause mellem doseringer (2 pauser ved 56 mg dosis og 3 pauser ved 84 mg dosis). Det antages, at observationen for esketamin er ca. 90 minutter, mens det antages at en læge bruger 60 minutter på at håndtere administrationen af lægemidlet. Det antages yderligere, at patienterne vil have en halv times individuel konsultation med en reservelæge månedligt til at monitorere effekt af behandlingen, hvor Medicinrådets enhedsomkostninger igen benyttes.

Der er ikke antaget nogen administrationsomkostning i relation til OAD. Til estimering af monitoreringsomkostning for OAD har ansøger taget udgangspunkt i TRIDEN-studiet. Her

findes det, at patienter i behandling med SSRI/SNRI gennemsnitligt har 9,75 besøg inden for psykiatrien årligt. Omkostning for disse opgøres ved DRG-taksten for ambulante besøg, således at den månedlige omkostning bliver 1.580 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Fagudvalget vurderer, at monitorering af behandling med esketamin minimum kræver et ambulant besøg hver gang lægemidlet skal doseres, og når der skal følges op på effekt af behandlinger ved konsultationer. Samtidig vurderes det, at omkostninger for det ambulante besøg bør opgøres ved den ambulante DRG-takst på 1.944 kr. pr. patient, således at kun sygeplejersketiden fordeles på flere patienter. Der er desuden stor usikkerhed omkring, hvor mange patienter sygeplejersken kan observere samtidig. Omkostninger for administration af esketamin kan findes i Tabel 13.

Tabel 13. Administrationsomkostninger for esketamin

Ressourcebrug	Enhed	Omkostning pr. time [DKK]	Tid brugt pr. ressource [timer]	Antal patienter administreret pr. gang	Omkostning pr. patient [DKK]
Administration af lægemiddel	DRG for psykiatrisk ambulant besøg	1944	-	1	1.944
Efterfølgende observation	Sygeplejerske timeløn (enhedsomkostning)	554	1,5	3	277

Fagudvalget vurderer desuden, at standardbehandling med esketamin vil kræve et øget behov for lokaler på ambulatorierne. Ansøger har ikke inkluderet disse omkostninger i modellen. Medicinrådet har ikke kunnet finde estimater på sådanne omkostninger.

Medicinrådet accepterer ansøgers antagelser vedr. administration og monitorering af patienter i behandling med OAD.

Medicinrådet accepterer ansøgers antagelser vedr. postdosisobservation, men ændrer omkostningen for administration og monitorering af esketamin til 1.944 kr. pr. patientbesøg.

Bivirkningsomkostninger
Bivirkningsfrekvenser for esketamin + OAD og OAD er i ansøgers analyse baseret på frekvenserne fundet i TRANSFORM-2 studiet, hvormed det antages, at det kun er i den akutte fase, at lægemidlerne er associeret med behandlingskrævende bivirkninger. Bivirkningsfrekvenser er i dette studie ikke opgjort separat for de to populationer, beskrevet i klinisk spørgsmål 1 og 2, hvorfor frekvenserne antages at være ens for de to populationer.

Ansøger antager ydermere, at det kun er bivirkningen dissociation, der kræver behandling. Her antages det, at bivirkningen medfører en omkostning på 780 DKK for en times konsultation med en reservelæge.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet vurderer, at håndteringen af bivirkningen dissociation varetages ved de generelle monitoreringsbesøg for esketamin + OAD og OAD. Omkostninger til bivirkninger sættes derfor til 0 DKK i Medicinrådets analyse.

Medicinrådet sætter bivirkningsomkostninger til 0 DKK.

4.2.3 Patientomkostninger

For både esketamin + OAD og OAD estimeres patientomkostninger i forbindelse med administration af lægemidler, monitoreringsomkostninger samt de sygdomsrelaterede omkostninger, beskrevet i afsnit 4.2.2. Dette inkluderer den effektive tid på hospitalet, ventetid og transporttid. Ansøger anvender en timeomkostning på 179 DKK og transportomkostninger på 100 DKK pr. besøg, baseret på Medicinrådets værdisætning af enhedsomkostninger[11].

For de sygdomsrelaterede omkostninger antager ansøger, at en indlæggelse varer 24 timer, mens ambulante besøg antages at vare 30 minutter.

Patienttid i forbindelse med administration og postdosisobservation af esketamin vurderes at tage 110 minutter pr. behandling (se Tabel 14).

Tabel 14. Patient- og transportomkostninger for administration af esketamin

Antal minutter pr. administration [minutter]	Timer pr. session [timer]	Transport pr. session [DKK]	Omkostninger pr. session [DKK]
110	1,83	**100**	**428**

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Der er usikkerheder omkring estimeringen af patienttid for sygdomsrelaterede omkostninger, da antagelserne er baseret på TRIDEN-studiet, der inkluderer patienter med mild, moderat og svær depression. Det har dog ikke været muligt at finde andre kilder, der estimerer patienttid for behandlingen. Yderligere vurderes det, at patienttid for MSM ≥ 9 populationen nok vil være større end for den samlede population, som følge af deres dårligere tilstand, men at det ikke har været muligt at finde data, der kunne belyse dette.

Det bemærkes, at modellen ikke tager højde for patientomkostninger i forbindelse med monitorering af lægemiddelbehandling. Dette vurderes dog at have minimal betydning for analysens resultat, da både esketamin + OAD- og OAD-patienter bliver monitoreret 1 gang om måneden.

Medicinrådet accepterer ansøgers estimerede patienttid.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet følsomhedsanalyser, der undersøger effekten af variation i en lang række af parametrene, der indgår i modellen heriblandt transitions-sandsynlighederne, sygdomsrelaterede omkostninger for de enkelte stadier, gennemsnitlig forbrug af esketamin pr. session og antal behandlinger pr. uge. Hvor det har været muligt, er der taget udgangspunkt i øvre og nedre grænse af konfidensintervallet for variationen af den givne parameter. I de tilfælde hvor dette ikke har været muligt, er variationen af parameteren baseret på antagelser.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger at præsentere ansøgers følsomhedsanalyser, der undersøger betydningen af ændringer i sygdomsrelaterede omkostninger for de enkelte stadier samt betydningen af ændringer af esketamins gennemsnitlige dosis og frekvens.

Yderligere vælger Medicinrådet at præsentere en følsomhedsanalyse, hvor der for effekt af behandling i den akutte fase tages udgangspunkt i TRANSFORM-2, fremfor at benytte poolede data fra TRANSFORM- 1, 2 og 3. Der præsenteres ligeledes følsomhedsanalyser, hvor behandlingsvarigheden med esketamin ændres. Disse analyser er taget med, da der i analysen er stor usikkerhed om den faktiske størrelse af disse parametre. Oversigt over følsomhedsanalyser for MSM ≥ 9 populationen kan findes i Tabel 15, mens oversigt over følsomhedsanalyser for den fulde patientpopulation kan findes i Bilag.

Tabel 15. Følsomhedsanalyser inkluderet i Medicinrådets analyse for MSM ≥ 9 populationen

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 1: Stigning i sygdomsrelaterede omkostninger baseret på øvre grænse af konfidensinterval	Omkostning pr. cyklus i modellens stadier øges for MSM ≥ 9 populationen på følgende måde: MDE: 5.654 DKK til 8.425 DKK *Response*: 3.226 DKK til 4.806 DKK *Remission*: 797 DKK til 1.188 DKK *Recovery*: 797 til 1.188 DKK
Følsomhedsanalyse 2: Reduktion i sygdomsrelaterede omkostninger baseret på nedre grænse af konfidensinterval	Omkostning pr. cyklus i modellens stadier sænkes for MSM ≥ 9 populationen på følgende måde: MDE: 5.454 DKK til 2.884 DKK *Response*: 3.226 DKK til 1.645 DKK *Remission*: 797 DKK til 407 DKK *Recovery*: 797 DKK til 407 DKK
Følsomhedsanalyse 3: Stigning i antal sessioner pr. uge hvor der behandles med	Sessioner ændres som beskrevet i nedenstående for MSM ≥ 9 populationen

Følsomhedsanalyse	Beskrivelse
esketamin baseret på øvre grænse af konfidensinterval	Akut fase: 1,92 til 2,11 sessioner pr. uge Uge 5-8: 1,0 til 1,1 sessioner pr. uge *Remission*: 0,72 til 0,8 sessioner pr. uge *Recovery*: 0,62 til 0,68 sessioner pr. uge
Følsomhedsanalyse 4: Reduktion i antal sessioner pr. uge hvor der behandles med esketamin baseret på nedre grænse af konfidensinterval	Sessioner ændres som beskrevet i nedenstående for MSM ≥ 9 populationen Akut fase: 1,92 til 1,73 sessioner pr. uge Uge 5-8: 1,0 til 0,9 sessioner pr. uge *Remission*: 0,72 til 0,65 sessioner pr. uge Recovery: 0,62 til 0,56 sessioner pr. uge
Følsomhedsanalyse 5: Stigning i gennemsnitlig esketamin dosis pr. session	Sessioner ændres som beskrevet i nedenstående for MSM ≥ 9 populationen Akut fase: 2,64 til 3 enheder brugt pr. session Uge 5-8: 2,72 til 3 enheder brugt pr. session *Remission*: 2,72 til 3 enheder brugt pr. session Recovery: 2,72 3 enheder brugt pr. session
Følsomhedsanalyse 6: Reduktion i gennemsnitlig esketamin dosis pr. session.	Dosis ændres som beskrevet i nedenstående for MSM ≥ 9 populationen Akut fase: 2,64 til 2 enheder brugt pr. session Uge 5-8: 2,72 til 2 enheder brugt pr. session *Remission*: 2,72 til 2 enheder brugt pr. session Recovery: 2,72 til 2 enheder brugt pr. session
Følsomhedsanalyse 7: Ændring af transitionssandsynligheder for den akutte fase	Effekt af behandling i den akutte fase baseres udelukkende på data fra TRANSFORM-2 for MSM ≥ 9 populationen
Følsomhedsanalyse 8: Ændring af sandsynlighed for loss of *response* og relapse ved behandling med OAD	Sandsynligheden for loss of *response* samt relapse sættes for OAD lig sandsynligheden associeret med esketamin + OAD for MSM ≥ 9 populationen
Følsomhedsanalyse 9: Transitionssandsynligheder sættes lig hinanden	Transitionssandsynlighed for OAD ændres, således at de er identiske med sandsynlighederne givet for esketamin + OAD for MSM ≥ 9 populationen
Følsomhedsanalyse 10: Stigning af behandlingslængde for esketamin	Andel af patienter der stopper behandling ved recovery ændres fra 50 % til 25 % for MSM ≥ 9 populationen

Følsomhedsanalyse	Beskrivelse
	Andel af patienter der stopper behandling efter 2 år ændres fra 50 % til 25 % for MSM ≥ 9 populationen
Følsomhedsanalyse 11: Reduktion af behandlingslængde for Esketamin	Andel af patienter der stopper behandling ved recovery ændres fra 50 % til 75 % for MSM ≥ 9 populationen. Andel af patienter der stopper behandling efter 2 år ændres fra 50 % til 75 % for MSM ≥ 9 populationen

4.4 Opsummering af basisantagelser

I Tabel 16 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 16. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Transitionssandsynligheder i akutte fase	Baseret på TRANSFORM-2	Baseret på poolede resultater af TRANSFORM-1, -2 og -3
Sandsynlighed for *response*/*remission* ved efterfølgende behandling	Baseret på de patienter der ikke opnår *response* i den akutte fase i Edwards et al.	Baseret på patienter der opnår *response* i den akutte fase samt dem som ikke gør i Edwards et al.
Andel der stopper behandling med esketamin ved indtræden i *recovery*-stadiet, MSM ≥ 9 populationen	70 %	50 %
Andel der stopper behandling med esketamin efter 2 år i behandling, MSM ≥ 9 populationen	99,9 %	50 %
Administration af esketamin	Takst for lønning af reservelæge	DRG-takst for ambulant besøg
Antal patienter en læge kan observere	3	1

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 16.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK pr. patient for den fulde patientpopulation (klinisk spørgsmål 1) og ca. [redacted] DKK for MSM ≥ 9 populationen (klinisk spørgsmål 2) i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 72.000 DKK for den fulde patientpopulation (klinisk spørgsmål 1) og ca. 81.000 DKK for MSM ≥ 9 populationen (klinisk spørgsmål 2).

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 17 og Tabel 18.

Tabel 17. Resultatet af Medicinrådets hovedanalyse, esketamin + OAD sammenlignet med OAD for den fulde patientpopulation (klinisk spørgsmål 1), DKK, diskonterede tal

	Esketamin + OAD	OAD	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Sygdomsrelaterede omkostninger	200.465	224.457	-23.991
Administrationsomkostninger	122.487	85.556	36.932
Patientomkostninger	189.864	197.344	-7.480
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 18. Resultatet af Medicinrådets hovedanalyse, esketamin + OAD sammenlignet med OAD for MSM ≥ 9 populationen (klinisk spørgsmål 2), DKK, diskonterede tal

	Esketamin + OAD	OAD	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Sygdomsrelaterede omkostninger	256.469	290.500	-34.031
Administrationsomkostninger	127.711	85.496	42.215
Patientomkostninger	196.403	197.206	-803
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 19. Resultatet af følsomhedsanalyserne for MSM ≥ 9 populationen kan ses i Tabel 19, mens følsomhedsanalyserne for den fulde patientpopulation kan findes i Bilag.

Tabel 19. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen (MSM ≥ 9), DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen, (MSM ≥ 9 population)	[redacted]
Følsomhedsanalyse 1: Stigning i sygdomsrelaterede omkostninger baseret på øvre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 2: Reduktion i sygdomsrelaterede omkostninger baseret på nedre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 3: Stigning i antal sessioner pr. uge hvor der behandles med esketamin baseret på øvre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 4: Reduktion i antal sessioner pr. uge hvor der behandles med esketamin baseret på nedre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 5: Stigning i gennemsnitlig esketamin dosis pr. session.	[redacted]
Følsomhedsanalyse 6: Reduktion i gennemsnitlig esketamin dosis pr. session	[redacted]
Følsomhedsanalyse 7: Ændring af transitionssandsynligheder for den akutte fase	[redacted]
Følsomhedsanalyse 8: Ændring af sandsynlighed for loss of *response* og relapse ved behandling med OAD	[redacted]
Følsomhedsanalyse 9: Transitionssandsynligheder sættes lig hinanden (svarende til ingen forskel i effekt)	[redacted]
Følsomhedsanalyse 10: Stigning af behandlingslængde for esketamin	[redacted]
Følsomhedsanalyse 11: Reduktion af behandlingslængde for esketamin	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at esketamin vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Esketamin bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Esketamin bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

For den fulde patientpopulation defineret i klinisk spørgsmål 1 antager ansøger, at der er 6.170 patienter i 2021, der kandiderer til behandling med esketamin. Dette estimat er baseret på data publiceret omkring andele af den danske population, der lider af moderat til svær depression, som samtidig er behandlingsresistente (defineret som at have fejlet på minimum to antidepressive behandlinger jf. afsnit 3.1). Stigning i patientpopulation antages at udvikle sig i takt med den generelle befolkningsvækst, således at andelen af personer i den samlede befolkning med behandlingsresistent depression forventes at være konstant. Til estimering af andele, der vil blive behandlet med esketamin, har ansøger benyttet egne data for markedsandele af lægemidlet Risperdal Consta® samt data fra TRIDEN-studiet på andele af patienter i den definerede patientpopulation, der modtager kombinationsbehandling af SSRI/SSRN og antipsykotika. Ansøger antager, at markedsandelen for esketamin vil ligge midt imellem disse to andele, og dermed estimeres markedsandelen til at være 4 % i år 1, 8 % i år 2, 11 % i år 3, 14 % i år 4 stigende til 16 % i år 5.

For MSM ≥ 9 populationen defineret i klinisk spørgsmål 2 antager ansøger, at der er 1000 patienter, der kandiderer til behandling med esketamin. Dette tal er baseret på Medicinrådets anbefalingsdokument i den initiale vurdering af esketamin. I tilfælde af anbefaling forventes det, at markedsandelen vil være højere for MSM ≥ 9 populationen end for den fulde patientpopulation, defineret i klinisk spørgsmål 1.Det antages, at markedsandelen vil være 25 % i år 1, 50 % i år 2, 69 % i år 3, 88 % i år 4 og 100 % i år 5.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

For den fulde patientpopulation, defineret i klinisk spørgsmål 1, anslår fagudvalget, at omkring 10.100 patienter vil være kandidater til behandling med esketamin i tilfælde af anbefaling[14]. Medicinrådet udarbejder derfor egen budgetkonsekvensanalyse, hvor fagudvalgets estimat på patientantal anvendes, mens ansøgers forventning til markedsoptag anvendes. Estimat af nye antal patienter pr. år for den fulde patientpopulation kan findes i Tabel 20. Medicinrådet accepterer ansøgers estimat på 1000 patienter samt ansøgers estimerede markedsandel for MSM ≥ 9 populationen . Estimaterne kan findes i Tabel 21.

Der udarbejdes en følsomhedsanalyse, der viser 100 % markedsoptag for at illustrere budgetkonsekvenserne, hvis alle potentielle patienter kom i behandling.

Medicinrådet udarbejder egen budgetkonsekvensanalyse for klinisk spørgsmål 1 og accepterer ansøgers budgetkonsekvensanalyse for klinisk spørgsmål 2. For begge populationer udarbejdes følsomhedsanalyser, der viser 100 % markedsoptag for at illustrere budgetkonsekvenserne, hvis alle patienter kom i behandling.

Tabel 20. Medicinrådets estimat af antal nye patienter pr. år for den fulde patientpopulation (klinisk spørgsmål 1)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Esketamin + OAD	404	808	1.111	1.414	1.616
OAD	9.696	9.292	8.989	8.686	8.484
			Anbefales ikke		
Esketamin + OAD	0	0	0	0	0
OAD	10.100	10.100	10.100	10.100	10.100

Tabel 21. Medicinrådets estimat af antal nye patienter pr. år for MSM ≥ 9 populationen (klinisk spørgsmål 2)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Esketamin + OAD	247	496	686	877	1000
OAD	753	504	314	123	0
			Anbefales ikke		
Esketamin + OAD	0	0	0	0	0
OAD	1000	1000	1000	1000	1000

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af esketamin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling til den fulde patientpopulation, defineret i klinisk spørgsmål 1. Anvendelse af esketamin til MSM ≥ 9 populationen,

defineret i klinisk spørgsmål 2, vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i hhv. Tabel 22 og Tabel 23.

Er analysen udført med AIP, bliver budgetkonsekvenserne hhv. ca. 116 mio. DKK og 81 mio. DKK i år 5.

Tabel 22. Medicinrådets analyse af totale budgetkonsekvenser for den fulde patientpopulation (kliniskspørgsmål 1), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 23. Medicinrådets analyse af totale budgetkonsekvenser for MSM ≥ 9 populationen (kliniskspørgsmål 2), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser men med antagelse om, at alle patienter i de relevante patientpopulationer overgår til behandling med esketamin fra år 1 efter en anbefaling, vil omkostningerne i år 5 være ca [redacted] DKK for den fulde patientpopulation defineret i klinisk spørgsmål 1, se Tabel 24. For MSM ≥ 9 populationen vil omkostningerne allerede fra år 1 være ca. [redacted] DKK (svarende til år 5 i hovedanalysen, hvor der antages en markedsandel på 100 %).

Tabel 24. Medicinrådets analyse af totale budgetkonsekvenser med antagelse om at hele patientpopulationen i klinisk spørgsmål 1 behandles med esketamin fra første år af anbefaling, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	År 1	År 2	År 3	År 4	År 5
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 25. Medicinrådets analyse af totale budgetkonsekvenser med antagelse om at hele patientpopulationen i klinisk spørgsmål 2 behandles med esketamin fra første år af anbefaling, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

For begge patientpopulationer er den inkrementelle omkostning i forbindelse esketaminbehandling i høj grad drevet af lægemidlets pris. Samtidig er de inkrementelle administrationsomkostninger også af betydelig størrelse, mens analysen peger på, at behandlingen kan betyde besparelser på sygdomsrelaterede omkostninger (psykiatriske indlæggelser, somatiske kontakter m.m.). Disse besparelser hænger sammen med, at patienterne ved behandling med esketamin estimeres at befinde sig kortere tid i omkostningstunge stadier sammenlignet med patienter, som kun behandles med OAD.

Indikationen for esketamin er, at behandling anbefales i mindst 9 måneder, hvis patienten har et stabilt *response* eller opnår *remission*. Dog er det uvist, om patienterne i praksis vil fortsætte i behandling i længere tid. Det er ligeledes uvist, hvor stor en andel der vil være stoppet med behandlingen efter 36 uger. Behandlingslængden har meget stor betydning for analysens resultat, da det netop er lægemiddelomkostninger, der driver de inkrementelle omkostninger.

Analysen er behæftet med flere betydningsfulde usikkerheder.

Sandsynlighederne for *relapse* og *recurrence* er forbundet med usikkerhed grundet studieopbygningen af SUSTAIN-1, hvor det kun er patienter, der har haft effekt af esketamin i TRANSFORM-studierne, der fortsætter i SUSTAIN-1. Andelen af patienter, der får *relapse* og *recurrence*, har betydning for analysens resultat, siden de medfører forskellige sygdomsrelaterede omkostninger. Yderligere er sandsynlighederne for

MSM ≥ 9 populationen baseret på et lille antal patienter, som forstærker usikkerheden i relation til besvarelse af klinisk spørgsmål 2.

Størrelsen af de sygdomsrelaterede omkostninger i de forskellige stadier er især for klinisk spørgsmål 1 behæftet med stor usikkerhed, da disse er baseret på TRIDEN-studiet, der inkluderer patienter med mild, moderat og svær depression. For MSM ≥ 9 populationen vurderes data bedre at afspejle de reelle omkostninger, da der her er taget udgangspunkt i de patienter i TRIDEN-studiet, der oplevede en svær depression. Disse sygdomsrelaterede omkostninger har også betydning for resultatet

På baggrund af studiernes opbygning vil det ligeledes være usikkert, hvordan dosisfordelingen (hhv. 56 mg eller 84 mg) vil være, og om patienterne vil modtage dosis én gang om ugen eller hver anden uge. Som det fremgår af følsomhedsanalyse 3-6 har dosis og frekvens betydning for analysens resultat.

Udover usikkerhederne i modellen der kan belyses ved følsomhedsanalyser, er der yderligere to betydningsfulde faktorer, modellen ikke tager højde for. Som allerede beskrevet, tager modellen ikke højde for genbehandling med esketamin i tilfælde af et tilbagefald, en behandlingsstrategi, der højst sandsynligt vil blive brugt, såfremt patienten har haft gavn af esketamin tidligere. Selvom det ikke er muligt at sige noget om omfanget, vurderes det, at den faktiske inkrementelle omkostning ved anbefaling af esketamin vil være højere, end modellen viser. Den anden faktor, modellen ikke tager højde for, er stigningen i omkostninger til infrastruktur i psykiatrien, som en anbefaling af esketamin vil medføre (lokaler o.lign.). Her er det heller ikke muligt at sige noget om omfanget, men også her vurderes det, at de faktiske inkrementelle omkostninger derfor vil være højere, end hvad modellen viser.

8. Referencer

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
2.0	15. december 2021	Ændret jf. Medicinrådets revurdering af esketamin.
1.0	26. august 2020	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK for den fulde population og ca. [redacted] DKK for hhv. den fulde patientpopulation og
MSM ≥ 9 populationen over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 26 og Tabel 27.

Tabel 26. Resultatet af ansøgers hovedanalyse for den fulde patientpopulation (klinisk spørgsmål 1), DKK, diskonterede tal

	Esketamin + OAD	OAD	Inkrementelle Omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Sygdomsrelaterede omkostninger	205.441	240.458	-35.017
Administrationsomkostninger	90.979	85.508	5.471
Patientomkostninger	188.006	197.235	-9.229
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 27. Resultatet af ansøgers hovedanalyse for MSM ≥ 9 populationen (klinisk spørgsmål 2), DKK, diskonterede tal

	Esketamin + OAD	OAD	Inkrementelle Omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Sygdomsrelaterede omkostninger	264.695	319.117	-54.422
Administrationsomkostninger	90.618	85.407	5.211
Patientomkostninger	189.925	197.002	-7.077
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af esketamin vil resultere i budgetkonsekvenser for den fulde patientpopulation på ca. [redacted] DKK i år 5 og ca. [redacted] DKK i år 5 for MSM ≥ 9 populationen. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 28 og Tabel 29.

Tabel 28. Ansøgers hovedanalyse for totale budgetkonsekvenser for den fulde patientpopulation (klinisk spørgsmål 1), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 29. Ansøgers hovedanalyse for totale budgetkonsekvenser for MSM ≥ 9 populationen (klinisk spørgsmål 2), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.3 Medicinrådets følsomhedsanalyser for den fulde patientpopulation

I Tabel 30 findes en beskrivelse af følsomhedsanalyserne foretaget for den fulde patientpopulation. Resultaterne af følsomhedsanalyserne kan findes i Tabel 31.

Tabel 30. Følsomhedsanalyser inkluderet i Medicinrådets analyse for den fulde patientpopulation

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 12: Stigning i sygdomsrelaterede omkostninger baseret på øvre grænse af konfidensinterval	Omkostning pr. cyklus i modellens stadier øges: MDE: 4582 DKK til 6828 DKK *Response*: 2614 DKK til 3895 DKK *Remission*: 646 DKK til 963 DKK *Recovery*: 646 til 963 DKK
Følsomhedsanalyse 13: Reduktion i sygdomsrelaterede omkostninger baseret på nedre grænse af konfidensinterval	Omkostning pr. cyklus i modellens stadier sænkes: MDE: 4582 DKK til 2337 DKK *Response*: 2614 DKK til 1333 DKK *Remission*: 646 DKK til 330 DKK *Recovery*: 646 DKK til 330 DKK
Følsomhedsanalyse 14: Stigning i antal sessioner pr. uge hvor der behandles med esketamin baseret på øvre grænse af konfidensinterval	Sessioner ændres som beskrevet i nedenstående Akut fase: 1,85 til 2,11 sessioner pr. uge Uge 5-8: 0,99 til 1,1 sessioner pr. uge *Remission*: 0,71 til 0,8 sessioner pr. uge *Recovery*: 0,675 til 0,68 sessioner pr. uge
Følsomhedsanalyse 15: Reduktion i antal sessioner pr. uge hvor der behandles med esketamin baseret på nedre grænse af konfidensinterval	Sessioner ændres som beskrevet i nedenstående Akut fase: 1,85 til 1,73 sessioner pr. uge Uge 5-8: 0,99 til 0,9 sessioner pr. uge *Remission*: 0,71 til 0,65 sessioner pr. uge Recovery: 0,675 til 0,56 sessioner pr. uge
Følsomhedsanalyse 16: Stigning i gennemsnitlig esketamin dosis pr. session	Sessioner ændres som beskrevet i nedenstående Akut fase: 2,64 til 3 enheder brugt pr. session Uge 5-8: 2,72 til 3 enheder brugt pr. session *Remission*: 2,72 til 3 enheder brugt pr. session Recovery: 2,72 3 enheder brugt pr. session
Følsomhedsanalyse 17: Reduktion i gennemsnitlig esketamin dosis pr. session.	Dosis ændres som beskrevet i nedenstående for MSM ≥ 9 populationen Akut fase: 2,53 til 2 enheder brugt pr. session Uge 5-8: 2,6 til 2 enheder brugt pr. session

Følsomhedsanalyse	Beskrivelse
	Remission: 2,6 til 2 enheder brugt pr. session Recovery: 2,57 til 2 enheder brugt pr. session
Følsomhedsanalyse 18: Ændring af transitionssandsynligheder for den akutte fase	Effekt af behandling i den akutte fase baseres udelukkende på data fra TRANSFORM-2
Følsomhedsanalyse 19: Ændring af sandsynlighed for loss of *response* og relapse ved behandling med OAD	Sandsynligheden for loss of *response* samt relapse sættes for OAD lig sandsynligheden associeret med esketamin + OAD
Følsomhedsanalyse 20: Transitionssandsynligheder sættes lig hinanden	Transitionssandsynlighed for OAD ændres, således at de er identiske med sandsynlighederne givet for esketamin + OAD

Tabel 31. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen (Fulde patientpopulation), DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen, (Fulde patientpopulation)	[redacted]
Følsomhedsanalyse 12: Stigning i sygdomsrelaterede omkostninger baseret på øvre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 13: Reduktion i sygdomsrelaterede omkostninger baseret på nedre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 14: Stigning i antal sessioner pr. uge hvor der behandles med esketamin baseret på øvre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 15: Reduktion i antal sessioner pr. uge hvor der behandles med esketamin baseret på nedre grænse af konfidensinterval	[redacted]
Følsomhedsanalyse 16: Stigning i gennemsnitlig esketamin dosis pr. session.	[redacted]
Følsomhedsanalyse 17: Reduktion i gennemsnitlig esketamin dosis pr. session	[redacted]
Følsomhedsanalyse 18: Ændring af transitionssandsynligheder for den akutte fase	[redacted]
Følsomhedsanalyse 19: Ændring af sandsynlighed for loss of *response* og relapse ved behandling med OAD	[redacted]

Scenarie	Inkrementelle omkostninger
Følsomhedsanalyse 20: transitionssandsynligheder sættes lig hinanden (svarende til ingen forskel i effekt)	[redacted]

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08.02.2022
MGK/CAF/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.02.2022
Leverandør	Janssen-Cilag A/S
Lægemiddel	Esketamin (Spravato)
Ansøgt indikation	Moderat til svær depression (MDD) hos voksne med manglende respons (revurdering)

Forhandlingsresultat

[redacted] I forhandlingen i forbindelse med revurderingen har Amgros opnået nedenstående pris [redacted] på esketamin såfremt esketamin anbefales af Medicinrådet.
[redacted]

[redacted]

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP* (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Esketamin	28 mg	1stk næsespray	1360,93	[redacted]	[redacted]	[redacted]
Esketamin	28 mg	2stk næsespray	2930,47	[redacted]	[redacted]	[redacted]
Esketamin	28 mg	3stk næsespray	4359,73	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)*	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Esketamin	28 mg	1stk næsespray	1360,93	[redacted]	[redacted]	[redacted]
Esketamin	28 mg	2stk næsespray	2930,47	[redacted]	[redacted]	[redacted]
Esketamin	28 mg	3stk næsespray	4359,73	[redacted]	[redacted]	[redacted]

[redacted]

Priserne er betinget af en anbefaling af klinisk spørgsmål 1 og/eller klinisk spørgsmål 2.
[redacted]

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området.
[redacted]

Status fra andre lande

Norge: Ikke anbefalet[1].
Sverige: Anbefalet til behandling af patienter med behandlingsresistens depression når andre muligheder er opbrugt[2].
England: Under evaluering[3].

Konklusion

Det er Amgros' vurdering at vi har fået den bedst mulige pris på esketamin, som det er muligt at opnå på nuværende tidspunkt.

[1] https://nyemetoder.no/metoder/esketamin-spravato

[2] https://janusinfo.se/download/18.13de125317a50669b3a54599/1625051143899/Esketamin-(Spravato)-210630.pdf

[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10371

Fra:	Koldby, Kasper [JACDK]
Til:	Ehm Astrid Andersson Galijatovic
Cc:	Camilla Vels Jensen; Christian Skouenborg; Johansen, Mikkel [JACDK]; Riise, Jesper [JACDK]
Emne:	Janssen høringssvar til vurderingsrapporten for Spravato til TRD
Dato:	21. januar 2022 14:25:16
Vedhæftede filer:	image001.png image002.png Janssen consultative response to the assessment of Spravato (21-01-2022).pdf

Kære Ehm,

Hermed fremsendes som aftalt høringssvar vedrørende vurderingsrapporten for Spravato til behandling af behandlingsresistent depression.

Vi berører i høringssvaret adskillige forskellige elementer i Medicinrådets vurdering af Spravato, men det er særligt relevant allerede her i mailen at fremhæve de to nedenstående, som specifikt relaterer sig til Medicinrådets konklusion på vurderingsrapporten:

- **Bivirkninger:** Medicinrådet skriver i den endelige konklusion: *"For begge patientpopulationer er der hyppige bivirkninger, herunder især neuropsykiatriske bivirkninger."* Vi argumenterer i vores høringssvar (side 2) for, at denne kommentar er i direkte modstrid med Fagudvalgets konklusioner i vurderingsrapporten, og vi appellerer derfor kraftigt til Medicinrådet om at genvurdere dette element i konklusionen med udgangspunkt i de samme stringente evidenskriterier, som Fagudvalget og Sekretariatet har anvendt gennem vurderingsrapporten.

- **Klinisk spørgsmål 2 (MSM ≥ 9):** Medicinrådet skriver i den endelige konklusion: *"*(...) *da data er yderst sparsomme, kan Medicinrådet ikke vurdere effekten af esketamin for denne patientgruppe."* Vi argumenterer i vores høringssvar (side 2) for, at denne kommentar ikke reflekterer Fagudvalgets vurdering i rapporten. Fagudvalget anerkender, at merværdien af Spravato ikke kan kategoriseres med udgangspunkt i Medicinrådets metoder, men de skriver specifikt, at data indikerer, at Spravato kan have en gavnlig effekt for patienter med svær TRD, og Fagudvalgets entydige vurdering er (side 52 i vurderingsrapporten), at Spravato er en relevant behandlingsmulighed for denne population, når andre behandlingsmuligheder er blevet afprøvet eller udelukket. Vi opfordrer derfor Medicinrådet til at genoverveje dette element i konklusionen, så den i højere grad afspejler Fagudvalgets vurdering af Spravato som et relevant behandlingsalternativ til denne gruppe af patienter med svær TRD, hvor der er akut behov for flere forskellige behandlingsmuligheder, da ikke alle patienter responderer på den samme behandling.

Afsluttende vil vi gerne i forbindelse med anbefalingen for Spravato på rådsmødet d. 23. februar anmode om, at Medicinrådet præsenteres for en **betinget anbefaling** som en alternativ mulighed i tilfælde af, at de ikke kan nå til enighed om en almindelig anbefaling af Spravato til patienter med svær TRD.
De omfattende patient- og samfundsomkostninger ved svær TRD samt det akutte behov for nye behandlingsmuligheder gør, at vi ikke betragter det som rimeligt over for denne oversete patientgruppe at afvente resultater af yderligere indsamling af data, før der gives en anbefaling om generel ibrugtagning af Spravato.
En betinget anbefaling kan fra dette perspektiv udgøre en mere formaliseret ramme for yderligere indsamling af data til at reducere de kliniske usikkerheder, som Fagudvalget har identificeret.

Du må som altid endelig bare tage fat i mig i tilfælde af uklarheder eller opfølgende spørgsmål.

De bedste hilsner,
Kasper

Kasper Magaard Koldby
Country HEMAR Manager

Janssen-Cilag A/S
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Birkerød, 3460 DK
Phone +45 29998303
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From: Ehm Astrid Andersson Galijatovic <EAG@medicinraadet.dk>
Sent: 14. januar 2022 13:26
To: Koldby, Kasper [JACDK] <KKoldby@ITS.JNJ.com>
Cc: Camilla Vels Jensen <cvj@medicinraadet.dk>; Christian Skouenborg <CSC@medicinraadet.dk>; Johansen, Mikkel [JACDK] <MJohan12@ITS.JNJ.com>; Bødker, Nikolaj [JACDK] <NBdker@its.jnj.com>; Riise, Jesper [JACDK] <jriise@ITS.JNJ.com>
Subject: [EXTERNAL] godkendt vurderingsrapport esketamin til TRD

Kære Kasper,

Hermed fremsendes den godkendte vurderingsrapport for esketamin til TRD.
Den sundhedsøkonomiske model blev ligeledes godkendt.
Vi planlægger som tidligere skrevet, at anbefalingen for esketamin behandles på rådsmødet i februar.
Jeres frist for høringssvaret er på fredag 21/1.

Mh Ehm

Med venlig hilsen

Ehm Andersson Galijatovic
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Medicinrådets behandling af personoplysninger

Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

Medicinrådet
Dampfærgevej 21-23, 3. floor
2100 København Ø

January 21st, 2022

Consultative response to the assessment of Spravato®

Upon the receipt of the Spravato® (esketamine) assessment report, Janssen considers it positive that the Medicines Council recognizes the unmet need in treatment resistant depression (TRD) and states that Spravato® in combination with SSRI or SNRI can have a clinically meaningful and sustained treatment effect in a severe subgroup of TRD patients with an imminent need for new treatment options. For severe TRD patients, all existing treatment options have been considered or tried with insufficient or no effect, and with Spravato® being the first antidepressant treatment indicated specifically for TRD in Europe, it constitutes a critical treatment opportunity. Fast access is crucial for these patients and should therefore be highly prioritized together with a commitment to build on the already solid evidence foundation and generate additional data and experiences from Danish patients and healthcare professionals (HCPs).

In the following, we will address some of the considerations that we perceive as critical to include in the assessment of Spravato® specifically, but also more generally when making decisions on the access to new treatments for the vulnerable and often neglected patient group with mental health disorders. To highlight the significant need for new treatment options for severe TRD patients, we will touch upon the following key topics:

- The substantial patient and societal burden of TRD with both significant direct and indirect costs to the individual patients, their relatives and society as a whole.
- Spravato® is the first breakthrough-drug within depression for more than 30 years and the first antidepressant treatment approved specifically for TRD in Europe.
- Fast access to new and innovative medicine is essential within an area with few or no other treatment alternatives.
- Improved treatments within depression is a political priority, and access to new treatments is a key factor in supporting this prioritization and improving patient outcomes.
- Several other European countries with similar guidelines as in Denmark have recognized the need for Spravato® and provided access for TRD patients.

Additionally, we will provide Janssen's perspective on some of the important topics addressed by the Medicines Council in the assessment of Spravato®, including the exclusion of the indirect comparison of Spravato® against RWE, the safety profile of the treatment and the additional evidence to be expected in the future. For the Expert Committee's decision to exclude the indirect analysis from the assessment of Spravato®, we would like to point out that

this exact analysis was a key element when the Medicines Council extraordinarily approved the re-submission for Spravato® based on the availability of new data.

The safety of Spravato® has been investigated in a comprehensive clinical trial program with more than 2,283 subjects treated with Spravato® across completed clinical studies, and the entirety of the safety data indicate that the safety profile of Spravato® is well characterized and tolerable within the proposed therapeutic dose range for use in a TRD population. The same conclusion was reached by EMA in their assessment report, and it is unambiguously confirmed by the Expert Committee in their assessment of Spravato® (page 43):

"Fagudvalget finder, at esketamin aggregeret ikke kan kategoriseres vedr. uønskede hændelser. Fagudvalget vurderer, at der ikke er betydende klinisk forskel mellem esketamin og placebo for andel af patienter, der oplever én eller flere SAE, og andel der ophører pga. uønskede hændelser indenfor 4 ugers behandling (...). Fagudvalget vurderer, ud fra den narrative gennemgang af data fra studier og EPAR, at der ikke er nævneværdig øget behandlingsophør grundet uønskede hændelser eller øget forekomst af dødsfald efter behandling med esketamin sammenlignet med placebo."

The Medicines Council's final conclusion states that "f*or begge patientpopulationer er der hyppige bivirkninger*", but, as clear from above quote, this claim is not supported by the Expert Committe's assessment nor is it substantiated with any available data. Janssen therefore strongly appeals to the Medicines Council to reassess this statement and, in doing so, apply the same rigorous evidence criteria as done throughout the assessment report. Furter, we encourage the Medicines Council to reconsider their conclusion regarding the subpopulation with MSM ≥ 9 score to make it reflect the assessment made by the Expert Committee. The Medicines Council states that the efficacy of Spravato® cannot be *assessed*, but even though the Expert Committee recognizes that the clinical value cannot be *categorized* within the methodological framework of the Medicines Council, their clear *assessment* is that Spravato® is a relevant treatment option to severe TRD patients (page 52):

"Ud fra fagudvalgets vurdering ville esketamin kunne være en aktuel mulighed, når følgende behandlinger har været forsøgt (eller er udelukket):

- *kognitiv terapi eller anden relevant form for psykoterapi*
- *andre strategier (augmentering med litium eller antipsykotika)*
- *ECT*
- *Isocarboxazid"*

The Need for New Treatment Options

Substantial Patient & Societal Burden

The burden attributed by mental disorders in general and depression in particular poses a massive challenge to the Danish society and is a major public health concern. This concern has only been reinforced by the COVID-19 pandemic, in which factors like anxiety, loneliness and social isolation have contributed to significantly increased depression prevalence rates and worsening of pre-existing psychiatric conditions (1-5). Depression is one of the most common psychiatric disorders and is the leading cause of disability worldwide. A significant proportion of patients with major depressive disorder (MDD) do not respond adequately to antidepressant treatment and develop TRD, which represents a key unmet need in the management of MDD. TRD is a serious, life-threatening condition with increased rates of suicide, hospitalization and impairment in daily functioning, and relapse rates are significantly higher relative to non-TRD (6, 7). In addition to depression being a debilitating disease for those affected, mental disorders were the overall contributor to loss of productivity including sick leave, reduced ability to work, and disability pension. In Denmark, the total costs related to treatment, care, and loss of productivity were DKK 31 billion annually from depression alone in 2015 (8). Moreover, a substantial burden is also experienced by family members or friends who are acting as caregivers, reducing the ability of caregivers to support themselves, and increasing their need for healthcare (9, 10). These indirect societal costs are not included in the assessment of Spravato®, but the extent of them nonetheless highlights the significant need for prioritizing new treatments within this disease area.

First approved antidepressant treatment for TRD

MDD is a highly recurrent psychiatric illness characterized by an increased risk of relapse with increasing frequency and severity of episodes over time, and the burden of TRD encompases considerable greater severity, chronicity, recurrence and admission to hospital than non-TRD. (11). Current antidepressant treatment options approved for the treatment of MDD target similar mechanisms within the monoaminergic system, but unfortunately shows limited improvement in a proportion of patients. This leaves many patients suffering from TRD and underlines the challenges that modern psychiatry faces. Further, the scientific evidence supporting the use of available MDD treatment strategies in TRD is limited, and often relies on evidence from older studies with less-stringent criteria of TRD (e.g. failure to repond to one prior treatment) that may not apply to patients with severe TRD (12). The insufficiency of empirical evidence beyond second-line treatment is supported by a recent meta-analysis concluding that despite its wide use in clinical practice, the evidence of augmentation strategies in TRD is sparse (12).

That psychiatry is in an urgent need of new pharmacological treatment options with a different mode of action is evident from the lack of major depression-drug breakthroughs for more than

three decades as well as the absence of medicines authorized specifically for TRD in Europe. Designated as a Breakthrough Therapy by the US Food and Drug Administration and approved by the European Commission on December 19th 2019, Spravato® nasal spray is the first antidepressant specifically indicated for TRD in Europe. The new mode of action combined with the unique route of administration result in a rapid response (as early as 24 hours) and maintained efficacy with clinically meaningful symptom improvement compared with currently available oral antidepressants in TRD patients.

The critical need for new treatment options and the relevance of Spravato® in severe TRD is also recognized by the Expert Committee in the clinical assessment (page 7).

"Spørgsmålet er stillet på baggrund af, at ***fagudvalget i den oprindelige vurdering bemærkede, at esketamin kunne være relevant til en særlig patientgruppe, som har prøvet adskillige alternativer*** *som TCA, monoaminoxidasehæmmere (isokarboxazid = Marplan), augmentering med lithium, quetiapin eller psykostimulantia og ECT, og hvor det derfor kan være relevant at forsøge med esketamin, hvis patienten er grundigt udredt forinden.* ***Disse patienter har et stort behov for alternative behandlings-muligheder"***

In the current resubmission, the Expert Committee has assessed Spravato® in a subpopulation of severe TRD patients with a Maudsley Staging Model (MSM) score of ≥ 9. We would like to remind the Medicines Council that the post hoc analyses of MSM ≥ 9 delivered represents a patient group where no prior scientific evidence exists for any current treatment used in Danish clinical practice. Although the clinical trials of Spravato® were not constructed based on the MSM ≥ 9 criteria and only include a proportion of the full patient population, data still indicate that Spravato® can have a beneficial treatment effect in combination with a SSRI or SNRI in severe TRD patients. The same conclusion is reached by the Expert Committee (page 52), supporting a recommendation of Spravato® in severe TRD patients:

"Ud fra fagudvalgets vurdering ville esketamin kunne være en aktuel mulighed, når følgende behandlinger har været undersøgt (eller er udelukket):

- *Kognitiv terapi eller anden relevant form for psykoterapi*
- *Andre strategier (augmentering med lithium eller antipsykotika*
- *ECT*
- *Isocarboxazid"*

Fast & Easy Access to New Treatments

With a proven potential to provide clinically meaningful and sustained improvements of depressive symptoms in severe TRD patients, the recommendation of Spravato® for these patients is in many ways an ethical and societal obligation. Moreover, a recommendation is in line with the principles for the prioritization of hospital medicines outlined by the Danish

Parliament as the foundation for all decisions being made in the Medicines Council (13). In particular, it supports the 5th principle of a fast introduction of new treatments and the 7th principle of equality in access to treatments based on patient needs. Fast access is especially crucial in the case of Spravato® due to the critical need for new treatment options within severe TRD, and a fast recommendation should therefore be highly prioritized together with a with a commitment to build on the already solid evidence foundation and generate additional data and experiences from Danish patients and HCPs.

Political Prioritization of Psychiatry

Additionally, a recommendation of Spravato® for Danish patients is also aligned with the increasing political and societal focus on the more general need for improvements in the treatment of patients with psychiatric disorders. The government's plan to develop a 10-year action plan for the psychiatry has been initiated in recognition of the fact, that the treatment of mental disorders has not been prioritized as much as treatment of other diseases – although the consequences can be just a serious for the patients and their relatives. (14). This is illustrated by a 15-20 years shorter life expectancy for people with mental disorders, and the recognition by Sundhedsstyrelsen that poor mental health is a risk factor for developing both somatic and mental disorders (15, 16). It is Janssen's position that efforts to improve treatments within psychiatry should focus on the entire patient pathway from prevention, early detection, diagnosis, treatment and rehabilitation. Fast and easy access to innovative treatment alternatives – medical as well as non-medical – is in our opinion a key factor in improving patient outcomes.

Reimbursement in Other European Countries

The importance of access to Spravato® as a new and innovative treatment option has already been recognized with positive reimbursement decisions being made in several other European countries with guidelines similar to Danish practice, including Sweden, Belgium, Netherlands, Italy and France. Many of these countries have had similar considerations as the Medicines Council in defining the patient population eligible for Spravato®, but they have recognized the overall treatment benefit of Spravato® and provided access for TRD patients. An overview with examples on these patient population criteria is provided below in Table 1.

Table 1. Examples of TRD patient populations reimbursed in other European countries

Country	TRD Patient Population Reimbursed
Sweden	The patient should have tried at least four treatment options for their depression before trying Spravato. For treatment with Spravato to be relevant, the patient should have tried the following treatment options: • At least two different antidepressants from two different drug classes • Adjuvant treatment with lithium or atypical antipsychotic drugs in antidepressant dosage In addition, the following should have been considered / tested before trying Spravato: • Electro-convulsive therapy (ECT) with unilateral and possibly bitemporal treatment • Transcranial magnetic stimulation • Adequate psychotherapy
Belgium	At least 2 different oral antidepressants, one of which should be augumentation or combination treatment
Netherlands	At least 3 different oral antidepressants
France	At least 2 different oral antidepressants, only patients from 18 year to 64 years
Scotland	At least 2 different oral antidepressants
Croatia	Patients with severe depression previously treated with at least 2 different oral antidepressants
Luxembourg	At least 2 different oral antidepressants
Italy	At least 2 different oral antidepressants
Ireland	At least 2 different oral antidepressants

Safety Profile of Intranasal Esketamine

The efficacy and safety of intranasal esketamine has been investigated in a comprehensive clinical trial program including more than 2,283 subjects treated with esketamine across completed Phase 1, Phase 2 and Phase 3 clinical studies. The entirety of the safety data taken together with the supporting evidence from the ongoing studies in TRD indicate that the safety profile of esketamine is well characterized and tolerable within the proposed therapeutic dose range for use in a TRD population. The same conclusion was reached by the EMA as outlined in the assessment report (page 158):

"*Taking into account the safety findings of the clinical trial program, intranasal administration of Esketamine in the target population with TRD at doses of 56 or 84 mg up to twice weekly was deemed to have an acceptable safety profile under the supervision of a healthcare professional" (17).*

Most TEAEs, including those most commonly occurring in the esketamine-treated subjects, were reported postdose on the day of intranasal study drug administration, and they were primarily transient in nature and resolved the same day (mostly within 2 hours) as expected by the pharmacological profile of esketamine. These observations were similar across the short-term and long-term completed Phase 2 and 3 TRD studies, and they are consistent with data from the ongoing long-term open-label Phase 3 study SUSTAIN-3 that based on the latest

clinical study report (December 7th, 2021) covers a mean total and cumulative duration of exposure to esketamine of 39.8 months, when including participant exposure in both the study and parent studies (18). That intranasal esketamine has an acceptable safety profile that is well tolerated was also recognized by the Medicines Council as stated on page 43 of the clinical assessment report:

*"Fagudvalget finder, at **esketamin aggregeret ikke kan kategoriseres vedr. uønskede hændelser**. Fagudvalget vurderer, at der **ikke er betydende klinisk forskel** mellem esketamin og placebo for andel af patienter, der oplever én eller flere SAE, og andel der ophører pga. uønskede hændelser indenfor 4 ugers behandling (...). Fagudvalget vurderer, ud fra den narrative gennemgang af data fra studier og EPAR, at **der ikke er nævneværdig øget behandlingsophør** grundet uønskede hændelser eller øget forekomst af dødsfald efter behandling med esketamin sammenlignet med placebo."*

We acknowledge the concern raised by the Medicines Council in relation to the specific adverse events as outlined in the clinical assessment report (e.g. dissociation, sedation and substance abuse potential). However, we would like to emphasize that these AEs were all identified as treatment-emergent adverse events (TEAEs) of special interest and implemented in the safety assessment of intranasal esketamine across the clinical trial program. As outlined in the very extensive safety section of the submission, these risks are well-characterized and mitigated through comprehensive risk minimization and pharmacovigilance activities outlined in the risk mitigation plan (RMP), and the periodic benefit risk evaluation reports (PBRERs). In line with the RMP, a Controlled Access Program (CAP) is approved by the Danish Health Authorities and implemented in Denmark with other additional risk minimization measures including distribution of educational materials informing prescribing physicians and patients about the identified risks and an HCP checklist to determine when patients are clinical stable and ready to leave the clinic. This checklist has been developed to support HCPs during the required post-administration observation period following an administration session per SmPC in line with the Medicines Council's recommendation.

As described in the submission, dissociation could appear with variable severity among subjects as highlighted by the Expert Committee. However, it is well-established that TEAEs of dissociation were primarily mild or moderate in severity and resolved on the same day (>95% of cases). None of the TEAEs in the completed Phase 2 and 3 TRD studies were reported as SAEs, and the dissociative symptoms occurred with decreasing rate over time by intranasal sessions. Discontinuation of treatment due to dissociative changes was only reported in isolated cases supporting the safety profile of esketamine.

The impact on blood pressure is extensively documented in the submission describing transient increases in systolic and/or diastolic BP shortly after esketamine administration that reaches a maximum within 40 minutes after drug administration (at the time of peak plasma

esketamine levels). These blood pressure elevations were generally transient (resolved 1.5 hours post-dose), asymptomatic and not associated with serious cardiovascular safety sequalae in line with the overall safety profile. As outlined by the Medicines Council, it is important to monitor BP after esketamine administration in line with the SmPC and RMP. Across clinical trials in the TRD population, 99% of the cardiovascular events were mild or moderate, and 90% or more of all reported TEAEs of "BP increased" occurred on the day of dosing and resolved spontaneously the same day. Discontinuation of esketamine treatment due to increased BP occurred at rates below 2% across all completed studies in TRD, which further supports esketamine's safety profile. As blood pressure increases can occur after esketamine administration, the drug is contraindicated in patients with cardiovascular and cerebrovascular conditions to whom blood pressure increases poses a serious risk.

Concerns related to substance abuse was also addressed comprehensively in the submission, showing no reports of drug-seeking behaviour and limited reporting of symptoms on the Physician Withdrawal Checklist-20-item (PWC-20) primarily of mild to moderate severity across studies. As shown in the long-term study SUSTAIN-2, no differences were reported between the treatment arms on the checklist with no evidence suggestive of a distinct withdrawal syndrome after cessation of dosing. This suggest that the drug abuse potential for patients with TRD alone is low. Risk minimization precautions for any potential risk of abuse, misuse and diversion associated with the self-administration of esketamine is addressed by a restricted medical prescription by psychiatrist only and the administration under direct supervision by an HCP in hospital settings (in- and out-patient). Further, the risk of drug abuse is mitigated with appropriate warnings and instructions in the EU PI, limited pack size and legal controls determined by the dispensing code A§4-BEGR in Denmark. The comprehensive risk minimization precautions have been recognized as suficient to provide patient access to esketamine in several other European countries, with the assessment in Ireland explicitly stating that *"the considerable administration and post-dose observation requirements for esketamine (Spravato®) were sufficient to alleviate concerns regarding misuse of this drug"* (19).

The sedative effects of esketamine are well-recognized, but generally mild to moderate in severity. Across all Phase 2 and 3 studies, the sedative effect had an onset shortly after the start of the dose and typically resolved spontaneously by 1 to 1.5 hours postdose. These TEAEs only led to treatment discontinuation in isolated cases, and they were reported as a SAE in only 1 subject across all Phase 2 and 3 studies. No symptoms of respiratory distress were observed, and hemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges. There were no TEAEs of respiratory depression among esketamine-treated subjects across the Phase 1, 2 and 3 studies, and none required cardiopulmonary resuscitation or other medical interventions. As esketamine may influence the ability to drive and use machines, HCPs should instruct patients before esketamine administration, in line with the SmPC and RMP, not to engage in potentially hazardous

activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day following a restful sleep.

Based on the data delivered to the Medicines Council, we strongly believe that the safety profile is well-characterized in a large patient population with long-term exposure to intranasal esketamine. As described, the solid data foundation has allowed for comprehensive risk minimization measures to be prepared, and we consider these an essential element when providing access to esketamine for Danish patients. The administration of esketamine in a controlled hospital setting is a key element in the minimization of risks, as it allows for potential adverse events to be resolved before the patients are discharged. Additionally, we recognize the need for the collection of additional safety data from a Danish clinical practice, and we encourage and welcome a continued collaboration on this to secure the best possible care for Danish patients.

Exclusion of Indirect Comparison

The Expert Committee has excluded the unanchored matching-adjusted indirect comparison (MAIC) of the long-term open-label safety study SUSTAIN-2 and the real-world evidence observational TRD-cohort study in the long-term comparative assessment of remission and response between intranasal esketamine and SSRI/SNRI based on the following statement:

"Fagudvalget vurderer, at analysen af SUSTAIN-2 vs. TRD ikke kan anvendes til at vurdere den vedvarende effekt af esketamin + OAD vs. placebo + OAD. Fagudvalget ønsker ikke at inkludere analysen SUSTAIN-2 vs. TRD i denne vurdering, fordi der er betydende forskelle i studiedesignet og i sammenligningen af et klinisk studie med en observationel kohorte."

The Expert Committee outlines several specific reasons for not accepting the comparison as valid. Before addressing each of these, it is pertinent to mention that the methodology of an indirect comparison (e.g. RCT vs observational cohort studies) is well recognized and accepted. In the absence of a randomized control trial, but where single-arm studies are available, an indirect comparison may be used to address certain evidence gaps. Indirect comparisons that meet a certain set of standards are accepted by many regulatory (EMA), HTA (NICE, CADTH) and medical organizations (WHO). In the case of Spravato®, an indirect comparison was performed to address an identified lack of longer-term comparative evidence of esketamine nasal spray to treatment strategies used for TRD. The studies used for the comparison were SUSTAIN-2 and a European observational TRD cohort. Janssen has access to detailed data for both these studies and as such was able to apply robust methods to account for any differences in the studies and to apply a strict set of data handling rules to ensure that as many study bias as possible could be considered and applying a conservative approach to the

esketamine nasal spray outcomes (see response to 3rd exclusion argument below for elaboration on the correction of bias).

The Expert Committee highlighted four reasons for not accepting the comparison:

1. *"I esketamin studierne **ses store placeboeffekter**, som fagudvalget vurderer ikke udelukkende skyldes opstart med ny OAD. Placeboeffekterne vurderes også at kunne skyldes forventning om ny effektiv behandling og mere interaktion med sundhedspersonale. En sammenligning mellem esketamin fra SUSTAIN-2 og et observationelt studie vil derfor overestimere effekten af esketamin, idet det ikke er muligt at justere for effekten af placebo*."

Due to the administration and observation requirements of esketamine nasal spray, there was a high level of HCP interaction in the SUSTAIN-2 clinical trial in line with the overall trial program. Janssen recognizes that some of the esketamine nasal spray treatment effect may be accounted for by the interaction with HCPs. However, compared to routine oral antidepressant treatments, esketamine nasal spray will per label require frequent interaction with HCPs in clinical practice, and even if the interaction does contribute to some of the overall treatment effect, this will also be the case in clinical practice. The amount of HCP contact seen in the SUSTAIN-2 trial reflects what will be required in a real-world setting, and also what is required according to the risk management plan. At the same time, the real-world comparison reflects the current treatment practice, and we therefore consider the comparison a fair reflection of what will be the benefit of treatment with Spravato® in the clinical practice.

2. *"I den observationelle TRD-kohorte **følges patienterne mindre tæt** end i det kliniske studie SUSTAIN-2, hvor patienterne følges ugentligt. Dette kan have stor betydning for både adhærens og den observerede effekt i studierne, idet fagudvalget forventer, at en tættere opfølgning vil have en positiv gevinst hos denne patientgruppe*."

We would like to remind the Medicines Council that the treatment paradigm for esketamine nasal spray is very different from that of currently available oral antidepressant regimes. Esketamine nasal spray must be self-administered under the direct supervision of a HCP, as such adherence to the treatment regime can be directly monitored and confirmed by the HCP. In contrast, oral antidepressants are typically taken at home and adherence to medication cannot be directly monitored. For the same reasons as described in the first point, due to the administration and observation requirements of esketamine nasal spray, patients will inadvertently be exposed to more follow-up and monitoring by their HCP. During the first 4 weeks of treatment, they will interact with their HCP twice per week and during maintenance 2-4 times per month. In contrast patients initiated on oral antidepressant regimes typically see their HCP less frequently (≤1 per month). For these reasons, monitoring of adherence and

follow up of esketamine nasal spray treatments are inadvertently greater than that of oral antidepressant regimes.

3. "***Response og remission er kun opgjort ved baseline og ved 6 måneder*** *for TRD-kohorten. Det er derfor ikke muligt at undersøge, om den kortvarige effekt ved 4 uger af OAD i TRD-kohorten er tilsvarende OAD + placeboarmen i esketaminstudierne. Dette ville være nødvendigt for at kunne kvalificere, om en eventuel langtidseffekt ville være sammenlignelig*"

Due to the observational nature of the cohort, frequent visits (as was done in SUSTAIN-2) were not permitted since this would not have been in line with clinical practice and the cohort would not have been considered observational. The only mandated visit in the cohort was at 6 months. For this reason, only a 6-month comparison was possible. Further, we would not expect the short-term effect of treatments in the TRD cohort to be equivalent to the OAD + placebo arm in the esketamine studies (as stated by the Expert Committee), due to the high placebo effect in the esketamine trials, which the Expert Committee recognizes. Because of the differences in how esketamine nasal spray is administered versus how routine treatments are given in the TRD cohort, there can be no true common comparator for an indirect comparison (high level of HCP interaction required for esketamine nasal spray). For this reason, an anchored indirect comparison was not possible, and an unanchored MAIC was performed. Since Janssen has access to detailed data for both studies, including a large number of patient baseline characteristics, it was possible to identify and adjust for 17 patient characteristic variables covering socio-demographics, disease severity, patient-reported outcomes, disease history (lifetime) and treatment history (in the current episode), and through this account for as many observed potential cofounders as possible in the indirect comparison.

4. "***I TRD-kohorten er der mindre opfølgning, og patienter kan frit skifte behandling eller lægge behandling oveni****, efter aftale med lægen, uden at det ellers påvirker deres deltagelse i studiet eller opfølgning negativt. I esketaminstudierne kan patienter også skifte væk fra esketamin, men det betyder, at de udgår af studiet og mister muligheden for at få den nye behandling, som måske havde givet dem en bedring af symptomer eller en forhåbning om dette. Fagudvalget vurderer, at incitamentet for at ændre behandling er forskelligt i de to studier. Dette kan påvirke effekten af esketamin, når den sammenlignes med effekten af OAD fra TRD-kohorten, fordi det i analyserne anses for non-response, hvis patienten har skiftet behandling eller fået lagt ny behandling oveni frem til de 6 måneder*"

Janssen also recognizes the different impacts of stopping treatment in the 2 studies, with those in the TRD cohort being able to continue in the study if they switched or altered their treatment and those in SUSTAIN-2 dropping out of the study if they ceased taking esketamine nasal spray. For this reason, dropouts/treatment changes were handled differently for the two

studies. In SUSTAIN-2, if a patient stopped taking esketamine nasal spray and dropped out of the study before month 6, they were imputed as a non-responder, even if they were a responder at the time of drop out. In the TRD cohort, patients who switched or altered their original baseline treatment in any way (e.g. combination with a new AD, augmentation with antipsychotics or mood stabilizers, etc.), were not imputed as non-responders. Their observed status at 6 months, either response or non-response, was considered regardless of any treatment changes that were made between baseline and 6 months. This approach to the TRD cohort data was taken to ensure patients who switched/altered their treatment for reasons other than efficacy were not penalized (for example, a patient may have responded to a treatment but is experiencing intolerable side effects and therefore may stop that treatment and switch to another but is still a responder). This method also ensured a very conservative approach in which we were accounting for some of the potential bias, since it allowed the best chance of capturing the positive efficacy outcomes from the TRD cohort, while applying stricter criteria to meet response/remission in SUSTAIN-2.

Finally, we would like to remind that the Medicines Council accepted the methodological validity of the unanchored MAIC for the resubmission of Spravato® and approved its use in the assessment of the long-term comparative efficacy of Spravato®. This approval was re-confirmed during the Medicines Council's quality assurance of the final submission. Excluding the methodology and the indirect comparison from the overall assessment is therefore not in line with the Medicines Council's own original pre-approval of the re-submission. While we recognize that an indirect comparison with an observational study is less robust than a direct RCT study comparison, we would like to emphasize that the data presented in the MAIC are in line with the results from the RCTs, hereby supporting the short and long-term beneficial effect of Spravato®. Thus, rather than rejecting the use of the indirect comparison entirely, the potential uncertainties described by the Medicines Council and recognized by Janssen could and should be accounted for during the assessment instead.

Data Expected in the Future

The most important uncertainties pointed out in the assessment of Spravato® by the Medicines Council were related to efficacy data, safety data, and treatment duration. Janssen is actively working to reduce these uncertainties and gain a better understanding of the clinical benefit of Spravato® to TRD patients by generating the following new data:

Updated data from the long-term studies (SUSTAIN-3)

- SUSTAIN-3 is a multicenter, open-label long-term extension study to evaluate safety, tolerability and efficacy of longer-term treatment (>1 year) with intranasal esketamine in TRD. The study population includes adults and elderly who previously participated in the phase 3 short-term or long-term studies. Safety data from the interim report of the

1,148 patients enrolled across 27 countries in the study has already been included in the re-submisison. However, the study is planned to continue to allow ongoing participants to continue to receive intranasal esketamine treatment if clinically warranted until it is available commercially in the participant's country, or December 2022, whichever is earlier. Final data on safety and efficacy is expected to be available in 2023 (20).

A new clinical study comparing Spravato® with combination therapy:

- ESCAPE-TRD is a randomized, open-label, rater-blinded, active-controlled, international, multicenter study to evaluate the efficacy, safety and tolerability of flexible dosed esketamine nasal spray compared with quetiapine extended-release in adults and elderly participants with TRD who are continuing a selective SSRI/SNRI. Inclusion and exclusion criteria are the same as in the studies that formed the basis for the marketing authorization. The study follows patients for up to 32 weeks with remission as the primary endpoint measured at week 8. This study will provide further evidence on the long-term effect and safety of Spravato® compared to standard augmentation treatment, and will also provide more quality of life data. The study has recently reached its recruitment target of 622 pateints and is currently ongoing in multiple clinical sites, including in Denmark, Norway, Finland and Sweden. The estimated study completion date is August 2022, and the expectation is to be able to deliver data from the study during 2023 (21).

Data from a European RWE study:

- Janssen is conducting a prospective, international, non-interventional cohort study of esketamine-nasal spray in treatment depression in Europe (ECHO), in which important data are collected on efficacy, safety and usage patterns in routine clinical practice in a broader population than previously studied. The study is planned to enroll approximately 450 patients, and it aims to provide insights into both dosing, frequency and treatment duration for intranasal esketamine in a clinical setting, as well as its impact on safety and the clinical, social and economic outcomes up to 6 months following the discontinuation of intranasal esketamine. All aspects of treatment and clinical management within the study, including dosing and treatment duration, must be in accordance with local clinical practice and at the sole discretion of the treating physician with no influence by the study. The data from the cohort will further substantiate the understanding of intranasal esketamine use in the treatment of TRD in participating European countries with the aim of improving guidance and informing the development of better treatment strategies. The study takes place in the countries where intranasal esketamine has been reimbursed and introduced, and it will be possible to include Danish patients in this study if desired. Data from the study are

expected to be available at the same time as data from ESCAPE-TRD and if Denmark is included, it will also be possible with separate analyses for Denmark.

Experience from Danish clinical practice:

- If Spravato® is recommended as a standard treatment option for severe TRD in Denmark, it will also be possible to collect data and experiences from Danish patients and clinicians. Janssen is committed to deliver safe and effective treatments to patients in need, and to support the Danish healthcare system achieving these goals. Thus, any collaboration to increase the evidence of intranasal esketamine in a Danish setting is highly welcomed and supported by Janssen.

Best regards,

Julie Brooker
Country Director Denmark
Janssen-Cilag A/S

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Medicinrådet

Medicinrådets revurdering af esketamin til behandling af behandlingsresistent depression hos voksne

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	13.01.2022
Dokumentnummer	130672
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet har vurderet esketamin i kombination med SSRI eller SNRI til to patientgrupper med varierende grad af behandlingsresistent depression. For begge grupper er der usikkerhed forbundet med vurderingen af esketamins effekt, fordi der ikke er komparative data for langtidseffekten. Derfor kan esketamin i kombination med SSRI eller SNRI ikke kategoriseres efter Medicinrådets metoder.

Medicinrådet vurderer, at esketamin ikke er et relevant behandlingsvalg for voksne patienter, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva. Det skyldes, at depression i dansk klinisk praksis ikke bliver vurderet behandlingsresistent efter tidligere behandling med blot to antidepressiva.

Medicinrådet vurderer, at patientpopulationen med en MSM-værdi ≥ 9 er mere repræsentativ for patienter med behandlingsresistent depression i dansk klinisk praksis, men da data er yderst sparsomme, kan Medicinrådet ikke vurdere effekten af esketamin for denne patientgruppe.

For begge patientpopulationer er der hyppige bivirkninger, herunder især neuropsykiatriske bivirkninger.

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MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standard-behandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

CI:	Konfidensinterval
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
MDD:	Major Depressive Disorder
HR:	*Hazard ratio*
ITT:	*Intention to treat*
MSM:	*Maudsley Staging Method*
NTT:	*Numbers Needed to Treat*
OAD:	*Oral Antidepressant*
OR:	*Odds ratio*
TRD	*Treatment Resistant Depression*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SNRI:	Serotonin-/noradrenalingenoptagelseshæmmer
SSRI:	Selektiv serotoningenoptagshæmmer
TCA:	Tricykliske antidepressiva

3. Introduktion

Formålet med Medicinrådets revurdering af esketamin til behandling af behandlingsresistent depression er at vurdere lægemidlets værdi sammenlignet med dansk standardbehandling i lyset af nye data på langtidseffekt og sikkerhed samt at vurdere værdien af esketamin for en særligt afgrænset patientpopulation med et stort behandlingsbehov. Medicinrådet modtog den endelige ansøgning til brug for revurderingen fra Janssen-Cilag 22. oktober 2021.

Tidligere har Medicinrådet vurderet esketamin (Spravato) i kombination med et SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode. I august 2020 besluttede Medicinrådet ikke at anbefale esketamin som mulig standardbehandling til denne indikation.

Revurderingen er udarbejdet, fordi Medicinrådet 18. december 2020 modtog en anmodning om at revurdere den tidligere anbefaling af esketamin på baggrund af, at der er kommet nye opdaterede data på sikkerhed og den vedvarende effekt.

Ved effektmål og vurderinger hvor der ikke er kommet ny data til, er tekst og vurderinger ikke ændret betydeligt i forhold til den oprindelige vurderingsrapport.

Revurderingen indeholder to kliniske spørgsmål, hvor klinisk spørgsmål 1 er identisk med den foregående vurdering, og klinisk spørgsmål 2 er nyt og vedrører en subgruppe med mere svær grad af sygdom, hvor sværhedsgraden af den depressive episode er defineret som patienter med *Maudsley Staging Method* (MSM) $\geq$ 9.

De to kliniske spørgsmål er:

Klinisk spørgsmål 1:

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

For dette kliniske spørgsmål forligger det samme 4 ugers korttidsdata fra TRANSFORM-1, -2, -3 og fra SUSTAIN-1, som også indgik i den seneste vurderingsrapport. Fagudvalget vil derfor kun tage stilling til, om vurderingen af sikkerhedsdata bør opdateres, og om der er ny relevant langtidsdata, som kan bruges til at vurdere effekten af esketamin ved 6 måneders opfølgning.

Klinisk spørgsmål 2:

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med moderat til svær behandlingsresistent depression vurderet ud fra MSM (MSM $\geq$ 9) i den aktuelle moderate til svære depressive episode?

Det kliniske spørgsmål er nyt og udgør en subpopulation af klinisk spørgsmål 1. Spørgsmålet er stillet på baggrund af, at fagudvalget i den oprindelige vurdering bemærkede, at esketamin kunne være relevant til en særlig patientgruppe, som har prøvet adskillige alternativer som TCA, monoaminoxidasehæmmere (Isokarboxazid = Marplan), augmentering med lithium, quetiapin eller psykostimulantia og ECT, og hvor det derfor kan være relevant at forsøge med esketamin, hvis patienten er grundigt udredt forinden. Disse patienter har et stort behov for alternative behandlings-muligheder.

3.1 Moderat til svær unipolar depression hos voksne

Moderat til svær unipolar depression eller Major Depressive Disorder (MDD) vil ifølge WHO, inden for en tidsramme af 20 år, være blandt de to mest belastende sygdomme i verden, hvad angår sygdomsbyrde og økonomiske konsekvenser for samfundet. I Danmark anslås prævalensen af moderat til svær depression blandt voksne at være ca. 3 %, svarende til ca. 111.000 voksne individer [1,2]. Det skønnes, at kun 65,3 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [2]. Ca. 14 %, svarende til ca. 10.100 voksne individer, har ikke en tilfredsstillende effekt af behandlingen [2,3] og er mulige kandidater til behandling med intranasal esketamin, jf. indikationen. Fagudvalget vurderer, at ca. 6000 patienter årligt henvises til ambulant behandling, og at der af disse er ca. 1000 behandlingsrefraktære patienter, hvor alle de gængse behandlingsmuligheder er afprøvet.

Depression viser sig på mange måder, men præsenterer sig typisk med symptomer som en følelse af at være trist og træt over længere tid, manglende selvværd, isolations-tendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og måske selvmords-tanker eller -planer. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [4].

Depression inddeles i mild, moderat og svær depression. Patienter med svær depression har en overhyppighed af selvmord, og tilbagefald er hyppige og forekommer med stigende frekvens afhængigt af, hvor mange depressioner man tidligere har haft [5]. Nogle får kronisk depression, hvor de depressive symptomer fortsætter igennem flere år [4]. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angst og personlighedsforstyrrelser og kan optræde parallelt til alvorlige fysiske lidelser som f.eks. diabetes, kræft og hjertesygdom. Herudover er misbrugsproblemer også almindeligt hos patienter med svær depression [4].

Depression kan udløses af længerevarende somatisk sygdom, stress, tab af nærtstående og eksistentielle kriser, men ofte er de udløsende faktorer ukendte. Genetisk prædisposition og personlighedsmæssige disponerende forhold bidrager til at øge risikoen for sygdommen [4]. Den nuværende medicinske behandling virker bl.a. ved at regulere signalstofferne serotonin og noradrenalin i hjernen. En stigende mængde evidens indikerer desuden, at dysregulering af glutamatsignaleringen i hjernen også kan være involveret i depression [6].

Hvis patienten med depression tidligere har haft maniske eller hypomane episoder, betegnes depressionen som en bipolar depression, der er led i en bipolar lidelse. En andel af patienterne med behandlingsresistent depression vil have en ikke-diagnosticeret bipolar depression, hvor de senere i forløbet vil udvikle mani eller hypomani [5,7].

Nogle patienter responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende. Ifølge Sundhedsstyrelsen omfatter behandlingsresistent depression voksne patienter over 18 år (både ambulante og indlagte) med moderat til svær depression, som diagnosticeres efter ICD-10 (WHO's diagnoseliste) kriterier eller er vurderet behandlingsresistent på *rating scale for treatment-resistant depression*, f.eks. *Maudsley Staging Method* (MSM) [8,9].

En af de største barrierer for forståelsen af behandlingsresistent depression er den manglende konsensus omkring definition og diagnosticering. Ifølge fagudvalget favner den hyppigst anvendte definition, bestemt efter ICD-10-kriterier, meget bredt, idet den omfatter patienter, som ikke har responderet på to forskellige typer antidepressiva, givet i tilstrækkelig dosis og i tilstrækkelig lang tid (≥ 4 uger) eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling. Risikoen ved at anvende disse kriterier er, at patienter diagnosticeres som behandlingsrefraktære for tidligt, dvs. før de er blevet tilbudt andre tilgængelige præparater eller behandlinger inkl. ikke-medicinske alternativer. En anden metode til at definere behandlingsresistent depression, som vinder indpas internationalt, er via spørgeskemaet MSM [9]. MSM er udviklet med henblik på at definere behandlingsresistens ved unipolar depression og anses for at have mere stringente kriterier end ICD-10, hvor det tilmed er muligt at inddele sværhedsgraden af behandlingsresistent depression. Den maksimale score for MSM er 15, og scoren er kategoriseret i mild: 3-6, moderat: 7-10 og svær 11-15 [9].

3.2 Esketamin

Esketamin, eller s-ketamin, er ét af to spejlmolekyler af ketamin (s- og r-ketamin). Brugen af s-ketamin fremfor r-ketamin forventes at øge specificiteten og derved mindske bivirkninger ved brug [10]. Esketamin udøver sin effekt i hjernen via N-methyl-D-aspartat (NMDA)-receptoren, der er et modtagermolekyle for glutamat. Glutamat frigives normalvis som et signalmolekyle i kontaktfladen mellem nerveceller i hjernen. Esketamin leder til en forbigående forøgelse i frigivelsen af glutamat, som trinvist fører til en forøgelse i neurotrofisk signalering, der er essentiel for nervecellernes funktion og overlevelse [6,11,12]. Dette antages at bidrage til at genoprette funktionen i hjerneområder involveret i reguleringen af affektiv og emotionel adfærd [6,11,12]. Esketamin, som ketamin, har dissociative effekter, der typisk efterlader brugeren med en følelse af at forlade kroppen [10]. Andre psykotomimetiske effekter er også beskrevet.

Til behandlingen af behandlingsresistent depression hos voksne er esketamin udviklet som en nasal formulering. Den intranasale administrationsvej er forbundet med en hurtig indsættende effekt, hvor det kan tage flere uger at opnå en ønsket effekt med de traditionelt anvendte *Oral Antidepressant* (OAD).

Denne revurdering omhandler indikationen: *Esketamin i kombination med en SSRI eller SNRI er indiceret til voksne med behandlingsresistent moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode* [13] .

Herudover har esketamin også indikation til akut korttidsbehandling, hvilket Medicinrådet vurderer i en særskilt proces.

Beslutningen om at ordinere esketamin skal afgøres af en psykiater. Esketamin er beregnet til selvadministration af patienten under direkte supervision af en sundhedsperson. En behandlingssession består af nasal administration af esketamin og en observationsperiode efter administrationen. Både administrationen og observationsperioden efter denne skal finde sted i passende kliniske omgivelser. På grund af muligheden for sedation, dissociation og forhøjet blodtryk skal patienten monitoreres af en sundhedsperson, indtil patienten anses for at være klinisk stabil og parat til at forlade klinikken [13].

Behandlingen med esketamin til behandlingsresistent depression omfatter en induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg eller 56 mg nasal esketamin (afhængigt af alder over/under 65 år) plus nyligt initieret daglig OAD, som ikke har indgået i behandling tidligere. Esketamin doseres herefter fleksibelt ud fra effektivitet og tolerabilitet (28 mg, 56 mg eller 84 mg). Efter 4 uger vurderes effekten af esketaminbehandlingen, og ved respons følger en optimerende behandlingsperiode med nasal esketamin (28 mg, 56 mg eller 84 mg), som administreres én gang ugentligt fra uge 5-8. Herefter følger en vedligeholdelsesfase, hvor esketamin administreres hver anden uge eller ugentligt. I alle faser administreres esketamin i kombination med det nyligt initierede OAD fra induktionsfasen [13].

Varigheden af esketaminbehandlingen er endnu uafklaret. Produktresuméet for esketamin anbefaler, at behandling af patienter, der oplever forbedring af deres depressive symptomer indenfor 4 uger, fortsætter deres behandling i minimum 6 måneder [13]. Under vedligeholdelsesfasen skal doseringen af esketamin individualiseres til den laveste hyppighed, der kan opretholde remission/respons. Behovet for fortsat behandling skal jævnligt reevalueres.

3.3 Nuværende behandling

Behandlingen af behandlingsresistent depression er ikke defineret i den gældende behandlingsvejledning for medicinsk behandling af unipolær depression, udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) i 2015 Behandlingsvejledning inklusiv lægemiddelrekommandation for medicinsk behandling af unipolar depression. I henhold til RADS' vejledning bør behandlingen af patienter med moderat til svær depression tilgås som følgende: Den indledende behandling af ikke-hospitaliserede patienter skal bestå af SSRI som førstelinjebehandling, der gives over 1-3 måneder. En fuld effekt af antidepressiva kan først ventes efter 4-6 uger. Opnår patienten en tilfredsstillende effekt ved behandlingen, fortsættes i en vedligeholdelsesfase i ca. 6-12 måneder eller længere, afhængigt af kliniske forhold. Hvis der ikke er tegn på bedring

efter ca. 2-4 uger på optimal dosis (i praksis ofte længere), skiftes der til andenlinjebehandling, som består af enten SSRI, SNRI, hæmmere af adrenerge receptorer (NaSSA) eller tricykliske antidepressiva (TCA). Er der fortsat ikke tegn på bedring, henvises der til psykiater eller indlæggelse på psykiatrisk afdeling. Blandt indlagte/hospitaliserede patienter med svær depression skal overvejes start med SNRI eller TCA. Dansk registerdata viser, at SSRI og SNRI er blandt de hyppigst anvendte tredjelinjebehandlinger i Danmark [3]. Behandlingsvarigheden varierer fra patient til patient.

Til patienter, der er refraktære overfor behandling med antidepressiva, overvejes en række alternativer eller tillæg til den medicinske behandling. Disse inkluderer: lysterapi, psykoterapi, elektrochok og i særlige tilfælde magnetstimulation. En national klinisk retningslinje vedrørende vanskelig behandlelig depression er udarbejdet i 2020 af Dansk Psykiatrisk Selskab og Region Hovedstadens Psykiatri (Guideline National Klinisk Retningslinje for vanskeligt behandlelig depression (dpsnet.dk)).

Målet med behandling af behandlingsresistent depression er at opnå remission af depressive symptomer, øge livskvaliteten og forhindre selvmord blandt en patientgruppe med øget selvmordstendens.

Depression og remission af depression måles ofte på sværhedsgraden af depressive symptomer på en skala som Hamilton Depression Rating Scale (HDRS) (interval 0-52 point) og Montgomery–Åsberg Depression Rating Scale (MADRS) (interval 0-60 point). HDRS er den mest almindelig anvendte depressionsskala på verdensplan, herunder også i Danmark. MADRS er udviklet med det formål at være mere følsom overfor de ændringer, der er forårsaget af antidepressiva, men der er en høj korrelation mellem de scorer, der opnås med hhv. HDRS og MADRS [14]. Remission defineres som hhv. ≤ 7 på HDRS-17 og ≤ 11 på MADRS [15,16] uanset udgangspunkt. Ved en halvering af symptomer på begge skalaer fra baseline er der tale om et respons.

4. Metode

Medicinrådets protokol for revurdering af esketamin til behandling af behandlingsresistent depression hos voksne beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

I Medicinrådes protokol er spørgsmål 1 identisk med foregående vurdering, mens spørgsmål 2 er nyt.

Spørgsmål 2 er stillet på baggrund af, at fagudvalget i den oprindelige vurdering bemærkede, at esketamin kunne være relevant til en særlig patientgruppe, som har prøvet adskillige alternativer som TCA, monoaminoxidasehæmmere (Isokarboxazid = Marplan), augmentering med lithium, quetiapin eller psykostimulantia og ECT, og hvor det derfor kan være relevant at forsøge med esketamin, hvis patienten er grundigt udredt forinden. Disse patienter har stort behov for alternative behandlingsmuligheder.

For begge kliniske spørgsmål ønsker fagudvalget at vurdere effekten ved hhv. 4 uger og ved 6 måneder for remission, respons, livskvalitet og bivirkninger/uønskede hændelser.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen baserer sig på syv fuldtekstsartikler, som rapporterer et fase 2-studie (SYNAPSE) og seks fase 3-studier (TRANSFORM 1, 2, 3 og SUSTAIN 1, 2 og 3), hvoraf SUSTAIN-3 er et extension-studie af de øvrige fem fase 3-studier. Herudover har ansøger inkluderet data fra to studier med observationel data (ATU og TRD).

Af disse studier indgik TRANSFORM-1, -2 og -3 samt SUSTAIN-1 i den oprindelige vurdering af esketamins effekt og sikkerhed, mens SUSTAIN 2 og SYNAPSE kun indgik i sikkerhed, fordi data var en del af EMAs EPAR.

SUSTAIN-3, ATU og TRD indgik ikke i den tidligere vurdering. Effektdata fra SUSTAIN-2 indgik heller ikke i den tidligere vurdering.

Det nye data er derfor:

1. Effektdata (korttidsdata) fra SYNAPSE
    a. anvendes ikke af fagudvalget til vurdering af effekt (se senere for en beskrivelse af årsag)
2. Effektdata ved 6 måneder fra SUSTAIN-2 (esketamin) og TRD (komparator)
    a. Data fra TRD anvendes ikke af fagudvalget (se senere for en beskrivelse af årsag)
3. Opdatering af sikkerhedsdata med data fra SUSTAIN-3 og ATU

Data fra SUSTAIN-3 og ATU er ikke publiceret.

Litteratursøgningen er i overensstemmelse med den, som er angivet i protokollen.

Tabel 1. Oversigt over studier inkluderet i ansøgers ansøgning

Klinisk studie, NCT-nummer, Referance	Studie design Længde	Intervention vs. komparator	Population	Anvendelse
TRANSFORM-1, NCT02417064 [17]	Randomiseret, dobbeltblindet, parallelgruppe, fase 3-studie -Screeningsfase: 4 uger -Introduktionsfase: 4 uger -*Follow-up* fase i 24 uger eller overførsel til SUSTAIN-1	Esketamin (fast dosis på 56 mg eller 84mg) + nyt OAD vs. placebo + nyt OAD	MDD-patienter i alderen 18-64 år med TRD ved randomiseringen (defineret som *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode)	Kortidsdata 4 uger. • Anvendes i meta-analyser. • Indgår i sikkerhed
TRANSFORM-2, NCT02418585 [18]	Randomiseret, dobbeltblindet, parallelgruppe, fase 3-studie -Screeningsfase: 4 uger -Introduktionsfase: 4 uger -*Follow-up*-fase i 24 uger eller overførsel til SUSTAIN-1	Esketamin (fleksibel dosis på 56 mg eller 84 mg) + nyt OAD vs. placebo + nyt OAD	MDD-patienter i alderen 18-64 år med TRD ved randomiseringen (defineret som *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode)	Kortidsdata 4 uger. • Anvendes i meta-analyser. • Indgår i sikkerhed
TRANSFORM-3, NCT02422186 [19]	Randomiseret, dobbeltblindet, parallelgruppe, fase 3-studie -Screeningsfase: 4 uger -Introduktionsfase: 4 uger -*Follow-up* fase i 2 uger eller overførsel til SUSTAIN-2	Esketamin (fleksibel dosis på 28 mg, 56 mg eller 84 mg) + ny OAD vs. placebo + ny OAD	MDD-patienter i alderen ≥ 65 år med TRD ved randomiseringen (defineret som *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode)	Kortidsdata 4 uger. • Anvendes i meta-analyser. • Indgår i sikkerhed
SUSTAIN-1, NCT02493868 [20]	Randomiseret, dobbeltblindet, relaps fase 3-studie -Introduktionsfase: 4 uger -Optimeringsfase: 12 uger -Varierende længde af vedligeholdelsesfase (median mellem 10-19 uger) -Overføres til SUSTAIN-3 i follow-up	Esketamin + nyt OAD i introduktions- og optimerings-fasen. Herefter randomiseres responderes 1:1 til esketamin + OAD eller placebo + OAD i vedlige-holdelsesfasen	MDD-patienter i alderen 18-64 år med TRD ved randomiseringen (defineret som *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode). *Responders* fra TRANSFORM-1 og -2	Effekt af esketamin ved 16 uger. Data kan desuden anvendes til at vurdere relapsrate for esketamin. Indgår i sikkerhed. Data gennemgås deskriptivt
SUSTAIN-2, NCT02497287 [21]	Open-label, *long-term* fase 3-studie -Screeningsfase: 4 uger -Introduktionsfase: 4 uger -Optimerings-/vedligeholdelsesfase: 48 uger -*Follow-up* i 4 uger eller overførsel til SUSTAIN-3	Esketamin + nyt OAD i introduktions-fasen. Herefter overføreres *responderes* til esketamin + OAD i optimerings-/vedlige-holdelsesfasen	MDD-patienter ≥ 18 år med TRD efter screeningsperioden (defineret som *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode). Derudover patienter fra TRANSFORM-3	Effekt af esketamin ved 6 måneder Indgår i sikkerhed. Data gennemgås deskriptivt
SUSTAIN-3, NCT02782104 (data on file)	open-label, *long-term*, *extension* fase 3-studie -Introduktionsfase: 4 uger -Optimerings-/vedligeholdelsesfasen var af varierende længde	Esketamin (fleksibel dosering)	Patienter som har gennemført TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1 eller SUSTAIN-2.	Indgår i sikkerhed. Data gennemgås deskriptivt

Klinisk studie, NCT-nummer, Referance	Studie design Længde	Intervention vs. komparator	Population	Anvendelse
SYNAPSE, NCT01998958 [22]	Dobbelt-randomiseret, placebo-kontrolleret, fase 2-studie -Screeningsfase: 4 uger -Dobbeltblindet behandlingsfase: 15 dag -Frivillig open-label fleksibel doserings fase: dag 15 – 74 -*Follow-up* fase: 8 uger	Esketamin (fleksibel dosering på 28 mg, 56 mg eller 84mg) vs. placebo	MDD-patienter i alderen 20-64 år med TRD ved screeningsperioden (defineret som *non-responders* på ≥ 2 OAD, hvoraf ét af disse *non-responders* skulle have været i den igangværende depressionsperiode)	Indgår i sikkerhed
ATU (data on file)	Fransk "cohort" data	Esketamin 28 mg	MDD-patienter over 18 år med TRD, som var *non-responders* på ≥2 OAD i igangværende depressionsepisode og hvor ECT ikke var en mulighed	Indgår i sikkerhed
TRD-kohorte studie, NCT03373253 [23]	Europæisk prospektivt observationel kohorte studie	Både farmaceutiske og/eller ikke farmaceutiske antidepressive behandlinger	MDD-patienter i alderen 18-74 år med TRD (defineret som patienter som har været *non-responders* på ≥ 2 OAD i samme depressionsepisode)	Effekt af anden antidepressiv behandling end esketamin ved 6 måneder. Data anvendes ikke i vurderingen af esketamin (se afsnit 5.2)

TRD = Treatment Resistant Depression

Gennemgang af studier

TRANSFORM-1 var et internationalt, multicenter, dobbeltblindet, parallelgruppe, randomiseret fase 3-studie. Studiet havde til formål at evaluere effekten, sikkerheden og tolerabilitet af to faste doser af intranasal esketamin, plus nyt OAD overfor behandling med intranasal placebo, plus nyt OAD hos MDD-patienter i alderen 18-64 år, som var *non-responders* på ≥ 1 og ≤ 5 OAD i igangværende depressionsperiode [17]. Studiet inkluderede en 4 ugers screeningsfase, hvorefter patienter som var *non-responders* på ≥ 2 OAD i den igangværende depressionsepisode blev overført til introduktionsfasen. Patienterne (n = 346) blev randomiseret 1:1:1 til placebo (n = 113), 56 mg eller 84 mg esketamin (n = 115/116) to gange ugentligt. Intervention og komparator blev administreret i kombination med et nyt OAD. Den nye OAD blev administreret open-label dagligt. Resultaterne blev opgjort efter en 4 ugers induktionsfase. Responderes fra alle arme kunne gå videre til vedligeholdelsesstudiet SUSTAIN-1 eller indgå i en 24 ugers *follow-up* fase, hvori alle *non-responders* også blev inkluderet. Det primære endepunkt for TRANSFORM-1 var ændring i MADRS totalscore, målt fra baseline i induktionsfasen til uge 4 (dag 28) eller sidste måling i induktionsfasen [17].

TRANSFORM-2 var et internationalt, multicenter, dobbeltblindet, parallelgruppe randomiseret fase 3-studie. Studiet havde til formål at evaluere effekten, sikkerheden og tolerabilitet af to fleksible doser (56 mg eller 84 mg) af intranasal esketamin, plus nyt OAD overfor behandling med intranasal placebo, plus nyt OAD hos MDD-patienter i

alderen 18-64 år, som var *non-responders* på ≥ 1 og ≤ 5 OAD i igangværende depressionsperiode [18]. Studiet inkluderede en 4 ugers screeningsfase, hvorefter patienter, som var *non-responderes* på ≥ 2 OAD i den igangværende depressionsepisode, blev overført til introduktionsfasen. Patienterne (n = 227) blev randomiseret 1:1 til fleksibel dosis esketamin (56 mg/84 mg; n = 116) eller placebo (n = 111) to gange ugentligt. Intervention og komparator blev administreret i kombination med et nyt OAD. Den nye OAD blev administreret *open-label* dagligt. Resultaterne blev opgjort efter en 4 ugers induktionsfase. Responderes fra alle arme kunne gå videre til vedligeholdelsesstudiet SUSTAIN-1 eller indgå i en 2-24 ugers *follow-up* fase, hvori alle *non-responders* også blev inkluderet. Det primære endepunkt var som for TRANSFORM-1.

TRANSFORM-3 var et multicenter, dobbeltblindet, parallelgruppe, randomiseret fase 3-studie. Studiet havde til formål at evaluere effekten, sikkerheden og tolerabilitet af 3 fleksible doser (28 mg, 56 mg, eller 84 mg) af intranasal esketamin, plus nyt OAD overfor behandling med intranasal placebo, plus nyt OAD hos ældre MDD-patienter over 64 år, som var *non-responders* på ≥ 1 og ≤ 8 OAD i igangværende depressionsperiode [19]. Studiet inkluderede en 4 ugers screeningsfase, hvorefter patienter, som var *non-responderes* på ≥ 2 OAD i den igangværende depressionsepisode, blev overført til introduktionsfasen. Patienterne (n = 138) blev randomiseret 1:1 til fleksibel dosis esketamin (28 mg/56 mg/84 mg; n = 72) eller placebo (n = 65) 2 gange ugentligt. Intervention og komparator blev administreret i kombination med et nyt OAD. Det nye OAD blev administreret dagligt og var *open-label*. Resultaterne blev opgjort efter en 4 ugers induktionsfase. Patienterne kunne gå videre til vedligeholdelsesstudiet SUSTAIN-2 eller indgå i en 2 ugers *follow-up* fase. Det primære endepunkt var det samme som i TRANSFORM-1 og -2.

SUSTAIN-1 var et internationalt, multicenter, dobbeltblindet, randomiseret, relaps fase 3-studie. Studiet sammenligner effekt, sikkerheden og tolerabilitet af fortsat intranasal esketaminbehandling (fleksibel dosering), plus OAD med ophør af intranasal esketaminbehandling (overgår til intranasal placebo + OAD) hos patienter, der har opretholdt respons med intranasal esketaminbehandling gennem induktionsfasen (4 uger) og optimeringsfasen (12 uger) [20]. SUSTAIN-1 inkluderede MDD-patienter mellem 18 og 64 år (n = 705), som var *non-responders* på ≥ 1 og ≤ 5 OAD i igangværende depressionsperiode. Patienterne indtrådte enten direkte i studiet (*direct-entry* patienter = 437) eller blev overført fra TRANSFORM-1 og -2 (*transferred-entry* patienter; n = 150/118). De patienter, som indtrådte direkte, gennemgik en screenings- og en induktionsfase tilsvarende den, som patienterne i TRANSFORM-2 gennemgik. De *direct-entry* patienter som oplevede respons blev overført til en 12-ugers optimeringsfase, hvor også de *transferred-entry* patienter blev overført til. Herefter blev de patienter, som oplevede fortsat respons eller remission, overført til vedligeholdelsesfasen. Her blev patienterne randomiseret 1:1 til fortsat intranasal esketamin + OAD (n = 152) eller intranasal placebo + OAD (n = 145). Varigheden af denne fase var individuel (median mellem 10 og 19 uger) og afhang af, hvornår patienten indtrådte i studiet, og hvornår et tilbagefald opstod (relaps). Fasen forløb, indtil et tilstrækkeligt antal patienter havde oplevet tilbagefald, baseret på statistiske styrkeberegninger. Det primære endepunkt for

SUSTAIN-1 var tid til tilbagefald for patienter i stabil remission efter behandling med esketamin i tidligere faser.

SUSTAIN-2 var et multicenter, open-label, *long-term*, fase 3-studie. Studiet havde til formål at evaluere langtidseffekterne og sikkerheden af esketamin (fleksibel dosering), administreret i kombination med nyt OAD [21]. SUSTAIN-2 inkluderede MDD-patienter over 18 år (n = 802), som var *non-responders* på ≥ 2 OAD i igangværende depressionsperiode. Patienterne indtrådte enten direkte i studiet (*direct-entry* patienter = 691) eller blev overført fra TRANSFORM-3 (*transferred-entry* patienter; n = 111). I den indledende 4 ugers screeningsfase, screenes de direkte indtrådte patienter. Herefter blev de patienter, som blev vurderet til at være *non-responders* på ≥ 2 OAD i igangværende depressionsepisode (enten via direkte observation eller via historiske data) overført til en 4 ugers *open-label* induktionsfase. I induktionsfasen blev alle direkte indtrådte patienter opstartet i en fleksibel intranasal esketaminbehandling (to gange ugentligt) + nyt OAD. I denne fase blev også *non-responders* fra TRANSFORM-3 studiet inkluderet. Disse patienter fik intranasal esketamin (to gange ugentligt) og fortsatte derudover den OAD-behandling, som de havde modtaget i TRANSFORM-3 studiet. Herefter blev alle patienter, der oplevede respons, overført til den 48-ugers optimerings-/vedligeholdelsesfase, hvor også *responders* fra TRANSFORM-3 blev inkluderet i studiet. Denne gruppe patienter fortsatte den esketamin + OAD-behandling, som de havde modtaget i TRANSFORM-3 eller opstartede esketaminbehandling, såfremt de havde modtaget placebo + OAD i TRANSFORM-3. Studiet blev afsluttet, da 300 patienter havde modtaget esketamin i 6 måneder, og 100 patienter havde modtaget esketamin i 12 måneder. Det primære endepunkt for SUSTAIN-2 var Treatment-Emergent Adverse Events (TEAEs) og bivirkninger. Der blev også opsamlet data på effekt ved MADRS score.

SUSTAIN-3 er et igangværende internationalt, multicenter, open-label, *long-term*, *extension* fase 3-studie, som har til formål at evaluere sikkerheden og langtidseffekterne af esketamin (fleksibel dosering) [24]. Studiet inkluderer patienter, som har gennemført TRANSFORM-1, -2 og -3 eller SUSTAIN-1 og -2. SUSTAIN-3 består af 2 faser; en induktions- og en optimerings-/vedligeholdelsesfase. I induktionsfasen inkluderes patienter fra TRANSFORM-1 og -2, som har gennemført en 6 måneders *follow-up* fase, patienter fra TRANSFORM-3, som var *non-responders* efter induktionsfasen i SUSTAIN-2, såvel som patienter fra SUSTAIN-1, som oplevede relaps i vedligeholdelsesfasen. I induktionsfasen modtager patienterne en fleksibel dosis af esketamin to gange om ugen i fire uger. Efter induktionsfasen overføres de patienter, som responderer på esketaminbehandlingen, samt *responders* fra TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1 eller SUSTAIN-2 til optimerings-/vedligeholdelsesfasen. Her fortsætter de overførte patienter med at modtage esketamin én gang om ugen i samme dosis som i det tidligere studie, bortset fra TRANSFORM-3, som fulgte et andet dosisregime. Efter fire uger i denne fase var det tilladt at tilpasse dosis til den enkelte patient. Optimerings-/vedligeholdelsesfasen er af varierende længde. Det primære endepunkt for SUSTAIN-3 var TEAEs og bivirkninger. Studiet er stadig i gang, og data fra dette studie er derfor fortrolige og endnu ikke publiceret.

SYNAPSE var et multicenter, dobbeltblindet, placebo-kontrolleret, dobbelt-randomiseret fase 2-studie, som havde til formål at evaluere effekt, sikkerheden og dosisrespons af

intranasal esketamin overfor intranasal placebo [22]. Studiet inkluderede MDD-patienter i alderen 20-64 år med TRD, defineret som utilstrækkelig respons på ≥ 2 OAD, hvoraf ét af disse skulle have været i forbindelse med en igangværende depressionsperiode. I alt havde 64 % af de inkluderede patienter kun modtaget én tidligere behandling i perioden. SYNAPSE bestod af fire faser; en screeningsfase, en dobbeltblindet behandlingsfase, en frivillig *open-label* fleksibel doseringsfase og en *follow-up* fase. I studiets 4 ugers screeningsfase blev patienternes respons på nuværende OAD vurderet. De patienter, som var *non-responderes* på ≥ 1 OAD i igangværende depressionsepisode, blev overført til den dobbeltblindet behandlingsfase på 15 dage, som var opdelt i to faser. I den første del af denne fase stoppede patienterne deres nuværende OAD-behandling og blev randomiseret 3:1:1:1 til intranasal placebo eller intranasal esketaminbehandling 28 mg, 56 mg eller 84mg, som blev givet på dag 1 og 4. I anden del af behandlingsfasen fortsatte de patienter, som havde modtaget placebo og kun havde milde til ingen depressions-symptomer med at modtage placebo. De patienter, der havde moderate til svære depressive symptomer, blev randomiseret 1:1:1:1 til placebo eller intranasal esketaminbehandling med 28 mg, 56 mg eller 84mg, som blev givet på dag 8 og 11. I den frivillige *open-label* fleksible dosserings fase modtog alle patienter intranasal esketamin fra dag 15 til 74, efterfulgt af en 8 ugers *follow-up* fase. Det primære endepunkt for SYNAPSE var ændringer fra basline målt på MADRS.

ATU var en "kohorte", der indsamlede data i Frankrig i forbindelse med en *Temporary Authorization for Use* (ATU) af intranasal esketamin 28 mg. Data blev indsamlet i perioden 23. september 2019 - 25. marts 2020. Kohorten inkluderede 71 MDD-patienter over 18 år med TRD, som var *non-responders* på ≥ 2 OAD i igangværende depressionsepisode, og hvor ECT ikke var en mulighed. I alt blev 54 patienters forløb dokumenteret. Data er fortrolige og ikke publicerede.

TRD var et europæisk prospektivt, ikke-interventionelt, observationelt kohortestudie, som inkluderede MDD-patienter mellem 18-74 år, som var *non-responders* på ≥ 2 OAD i den samme depressionsepisode [23]. I kohorten opstartede alle patienter (n = 411) en ny antidepressiv behandling, defineret som både farmaceutiske og/eller ikke farmaceutiske behandlinger. Denne behandling blev givet i kombination med eller som erstatning for en tidligere antidepressiv behandling. Interventionerne kunne ændres igennem studiet. Studiet bestod af baseline data, en 6-12 måneders observationsperiode samt en udvidet observationsperiode på op til 6 måneder, fra den sidste patient blev inkluderet. Utilsigtede hændelser blev ikke dokumenteret i selve studiet, men i pharma-overvågning. MADRAS-score og livskvalitet blev målt ved 6 måneder.

Studie- og populationskarakteristika
Baselinekarakteristika og overførbarhed til danske forhold gennemgås i det følgende.

Baselinekarakteristika
Korttidsstudierne (TRANSFORM 1-3): Baselinekarakteristika adskiller sig ikke nævneværdigt mellem studierne hvad angår MADRS-score, køn og antal tidligere behandlinger (se Tabel 2). Patienter i TRANSFORM-3 har en højere gennemsnitsalder end de øvrige TRANSFORM-studier, da det er studie i en ældrepopulation > 65 år. Forskelle i baselinekarakteristika består derudover i varighed af den indeværende depressive

episode (ca. 200 uger i TRANSFORM-1 vs. ca. 115 uger i TRANSFORM-2 og ca. 216 uger i TRANSFORM-3).

Langtidsstudierne (SUSTAIN 1 og2): Baselinekarakteristika adskiller sig ikke nævneværdigt mellem studierne, fraset SUSTAIN-1´s MADRS-score, som ligger lidt højere end MADRAS-scoren i SUSTAIN-2 (ca. 38 se Tabel 2).

Øvrige studier (SYNAPSE, ATU og SUSTAIN-3): Baselinekarakteristika er sammenlignelige, fraset varighed af den indeværende depressive episode (ca. 60 uger vs. 182 uger; se Tabel 2). Derudover er antal tidligere behandlinger kun opgjort for SYNAPS.

Tabel 2. Baselinekarakteristika for de indsendte studier

	TRANSFORM-1 (n = 342) [17,25]	TRANSFORM-2 (n = 223) [18,25]	TRANSFORM-3 (n = 137) [19,25]	SUSTAIN-1 (n = 297) [20,25]	SUSTAIN-2 (n = 802) [21]	SYNAPSE (n = 67) [22]	ATU (n = 66)	SUSTAIN-3 (n = 1148)
MADRS-score ved baseline (mean) [range]	37,6 (5,51) [18-53]	37,1 (5,67) [21-52]	35,2 (6,16) [19-51]	37,9 (5,50) [4*-53]	31,4 (5,39)	34,1 (5,11)	[redacted]	Ikke oplyst
Alder, år (mean (SD)	46,3 (11,9)	45,7 (11,89)	70,0 (4,52)	46,1 (11,10)	52,2 (13,69)	44,7 (10,04)	[redacted]	[redacted]
Kvinder, n (%)	241 (70,5)	138 (61,9)	85 (62,0)	193 (64,8)	502 (62,6)	38 (56,7)	[redacted]	[redacted]
Varighed af nuværende depressive episode, uger, mean (SD) [range]	202,9 (290,24) [6-2288]	114,6 (157,96) [ikke oplyst]	215,8 (341,71) [ikke oplyst]	132,2 (209,18) [9-1248]	Ikke oplyst	59,8 (63,5)	[redacted]	Ikke oplyst
Antal tidligere behandlinger med antidepressiva, indeværende depressions episode, n (%)								
1	31 (9,1)	27 (12,1)	21 (15,3)	208 (70,0)	17 (2,1)	43 (64,2)	Ikke oplyst	Ikke oplyst
2	174 (51,2)	123 (55,2)	63 (46,0)		465 (58)	15 (22,4)	Ikke oplyst	Ikke oplyst
3	94 (27,6)	46 (20,6)	30 (21,9)	87 (29,3)	187 (23,3)	9 (13,4)	Ikke oplyst	Ikke oplyst
4	34 (10,0)	20 (9,0)	16 (11,7)		133 (16,6)		Ikke oplyst	Ikke oplyst
5	6 (1,8)	4 (1,8)	5 (3,6)				Ikke oplyst	Ikke oplyst
6, 7, 8 eller 9	≤ 1 % i hver kategori	≤ 1 % i hver kategori	≤ 1 % i hver kategori				Ikke oplyst	Ikke oplyst

**En enkelt patient havde et dramatisk fald efter screeningperioden og frafaldt efter induktionsfasen.* Grå felter indikerer nye studier fra den oprindelige vurdering til revurderingen.

Kriterier for inklusion og eksklusion
Fagudvalget anser inklusions- og eksklusionskriterierne for esketaminstudierne (TRANSFORM 1, 2, 3 og SUSTAIN 1, 2, 3) som begrænsende ift. at kunne overføre studieresultaterne til dansk klinisk praksis.

Fagudvalget finder eksklusionskriteriet om, at patienterne ikke må have udvalgte psykiske sygdomme og komorbiditeter problematisk for overførbarheden til dansk klinisk praksis, da en betragtelig andel af de danske patienter vil lide af andre psykiske sygdomme og nogle også vil lide af somatiske komorbiditeter som kardiovaskulær sygdom og ukontrolleret forhøjet blodtryk.

På baggrund heraf har fagudvalget i protokollen for revurderingen af esketamin ønsket data for komorbiditet for de patienter, som indgik i studierne. Data ville kunne anvendes til at vurdere heterogeniteten i en studiepopulation og om studiepopulationen er repræsentativ for patienter med behandlingsresistent depression i Danmark.

Ansøger oplyser, at der ikke findes data for andelen af de inkluderede patienter, der havde somatiske komorbiditeter.

Fagudvalget vurderer, at andelen af angstlidelser og PTSD i studierne er i overensstemmelse med, hvad der kan forventes i den danske population, men fremhæver, at de danske patienter har yderligere og betydelige psykiatriske komorbiditeter, som ikke er repræsenteret i studiepopulationerne i TRANSFORM- eller SUSTAIN-studierne, blandt andet som følge af nedenstående eksklusionskriterier:

- nuværende eller tidligere DSM-5 diagnose for psykotiske tilstande
- MDD med psykose
- bipolær sygdom og lignende
- nuværende *obsessive compulsive disorder* (OCD)
- intellektuel disability (DSM-5 diagnostiske koder: 317, 318.0-2, 315.8, 319)
- autisme
- borderline, antisocial, histrionisk eller narcissistisk personlighedsforstyrrelse
- positiv urinprøve for udvalgte narkotika, herunder cannabinoider.

Det er fagudvalgets vurdering, at flere psykiatriske komorbiditeter typisk medfører en mere behandlingsresistent depression, og at tilstedeværelsen af ovennævnte psykiatriske komorbiditeter optræder relativt hyppigt i populationen.

Fagudvalget finder herudover, at inklusionskriteriet om, at patienterne kun skal have afprøvet min. 2 OAD betyder, at nogle patienter har haft depression i en for kort periode og fortsat har en række alternativer tilgængelige, før de er behandlingsrefraktære i en dansk kontekst. Fagudvalget anerkender, at patienterne i studierne falder under den anvendte definition på behandlingsresistent depression, men fremhæver, at definitionen er af mere praktisk karakter. Fagudvalget vurderer, at antal tidligere behandlinger er meget begrænset og mener, at det er usandsynligt, at patienter, der alene har haft

utilstrækkelig effekt af to tidligere behandlinger med OAD, vil blive vurderet behandlingsresistente i en dansk klinisk kontekst. I en dansk kontekst ville man for eksempel forvente, at patienterne, udover skift i OAD mere end 2 gange, også skulle have prøvet kognitiv terapi, ECT og augmentation med litium eller antipsykotika, før de ville blive vurderet behandlingsrefraktære.

Fagudvalget bemærker desuden, at tidligere *non-response* til ECT er et eksklusionskriterie i TRANSFORM 1, 2, 3 og SUSTAIN-1-2. Dette kan være problematisk, fordi mange danske behandlingsrefraktære patienter vil have prøvet ECT tidligere uden effekt. Patienter med *non-response* på ECT kan være sværere at bringe til remission, idet deres sygdom kan antages at have en større grad af refraktæritet.

Samlet set vurderer fagudvalget, at studiepopulationerne, på baggrund af de valgte inklusions- og eksklusionskriterier, i begrænset omfang afspejler de patienter, der vurderes behandlingsrefraktære i Danmark.

In- og eksklusionskriterier for TRD-kohorten svarer nogenlunde overens med esketaminstudierne, hvilket betyder, at de samme forbehold gør sig gældende. I TRD-kohorten var det dog tilladt at have fået ECT tidligere.

SYNAPSE-studiet inkluderede en andel af patienter, som ikke falder under den anvendte definition af behandlingsrefraktæritet. I alt havde 64 % af de inkluderede patienter kun modtaget én tidligere behandling i perioden.

Varighed af depression og tidligere behandlinger
Varighed af indeværende depressive periode kan være kort (helt ned til 6 uger, se baselinekarakteristika i Tabel 2) i studierne, jf. inklusionskriterierne. Varigheden er opgjort som middelværdi (mean) med et meget bredt spænd (range), hvorfor det er svært at vurdere, om forskellen mellem studier har klinisk relevans. SYNAPSE-studiet har en kortere varighed af depression end de øvrige studier.

Fagudvalget vurderer, at danske patienter med behandlingsresistent depression har en sammenhængende depressiv episode på minimum et år, men ofte mere. Generelt finder fagudvalget, at jo længere sygdomsvarighed, des sværere er det at behandle depressionen.

Samtidig behandling med oral antidepressiva
I TRANSFORM-1, -2, -3 og SUSTAIN-1, -2 studierne opstartes nye OAD samtidig med opstart af esketamin. Fagudvalget finder, at igangsættelse af to nye behandlinger (uafhængigt af hvilken behandling) simultant, som gjort i disse studier, er problematisk, idet det bliver uklart, hvorvidt effekterne hos den enkelte patient – gavnlige eller negative – kan tilskrives esketamin, OAD eller en kombination af disse. Fagudvalget anerkender, at denne tilgang er valgt af etiske årsager, men bemærker i øvrigt, at en mere rationel fremgangsmåde til behandling af den aktuelle population med esketamin i dansk kontekst ofte ville være at fortsætte en behandling med antidepressiva, som evt. giver en partielt respons hos patienten og herefter behandle med esketamin i tillæg.

Blinding
Esketamin har hos nogle patienter en dissociativ effekt, som opleves af patienter efter administration af lægemidlet. Dette er ikke muligt at efterligne hos patienter i komparatorgruppen, hvorfor blindingen ikke er optimal. En del patienter og personel har derfor i forbindelse med administration været klar over, om patienterne har fået administreret esketamin eller placebo. Dette forventes især at være tilfældet for placebogruppen i SUSTAIN-1, hvor patienterne tidligere vil have fået esketamin og dermed kender de umiddelbare virkninger af esketamin. Potentielle konsekvenser heraf inkluderer noceboeffekt, hvor negative forventninger til placebobehandling modvirker en effekt eller giver tilsyneladende bivirkninger. Det gælder for esketamingruppen, at patienter kan opleve placeboeffekt ved at kende til at få det aktive stof. Potentielle nocebo- og placeboeffekter og deres indvirkning på effektestimaterne kan ikke afklares yderligere.

5.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse beskrevet.

Protokollen definerer to relevante måletidspunkter (min. 4 uger og min. 6 måneder) for at belyse hhv. den hurtigindtrædende effekt og den vedvarende effekt af esketamin. Begge måletidspunkter er vurderet lige vigtige og vægtes ens, jf. protokollen.

Kortidseffekt (4 uger): Den endelige ansøgning inkluderer tre randomiserede kliniske studier (TRANSFORM-1, -2 og -3), som kombineres i en metaanalyse til at belyse effektforskellen efter 4 uger i en direkte sammenligning mellem esketamin, + OAD og placebo, + OAD. Data fra TRANSFORM-1, -2, -3 indgik ligeledes i den oprindelige vurdering, og der er derfor ikke foretaget betydende ændringer i konklusioner og tekst for klinisk spørgsmål 1 i forhold til den oprindelige vurdering.

Vedvarende effekt (6 måneder): I ansøgningen er inkluderet tre studier (SUSTAIN-1, SUSTAIN-2 og TRD-kohorte), som ansøger mener kan anvendes til at belyse den vedvarende effekt af esketamin ved 16 uger (SUSTAIN-1) og ved 6 måneder (SUSTAIN-2 og TRD). Ansøger gennemgår data fra SUSTAIN-1 narrativt, mens SUSTAIN-2 og TRD-kohorten kombineres i en indirekte analyse. Data fra SUSTAIN-1 indgik også i Medicinrådets oprindelige vurdering og er ikke ændret væsentligt.

Sikkerhedsdata: Udover de ovennævnte studier inkluderer ansøger tre studier (SUSTAIN-3, SYNAPSE og ATU), som anvendes til at belyse bivirkninger og sikkerheden ved brug af esketamin. Data fra disse studier bliver ligeledes gennemgået narrativt i ansøgningen.

Medicinrådet har foretaget følgende ændringer af ansøgers beregninger og resultatfremstilling:

Håndtering af missing data ved 6 måneder
Ansøger har på Medicinrådets opfordring udarbejdet beregninger for effektmålene, med nonresponder imputation analyses fremfor *Last Observation carrried forward* (LOCF).

Hvis muligt rapporterer Medicinrådet beregninger baseret på ”observed cases” og på ”nonresponder imputation analyses”.

Model i metaanalyse for korttidseffekten
For studierne TRANSFORM-1, -2, og -3 har fagudvalget, for samtlige effektmål, valgt at anvende en *random effects*-model i metaanalyserne i stedet for en *fixed effects*-model, som ansøger har anvendt i den endelige ansøgning. Baggrunden for dette er, at fagudvalget vurderer, at vilkåret for at anvende en fixed effects-model (homogenitet mellem studier og studiepopulationer) ikke er opfyldt: Studierne repræsenterer ikke samme aldersgrupper, og administrationen af esketamin er forskellig mellem studierne (dosisforskelle).

Hændelsesrater for korttidseffekt
Til beregning af de absolutte forskelle for sammenligning mellem esketamin og placebo efter 4 uger (TRANSFORM-1, -2, og -3) i klinisk spørgsmål 1 har fagudvalget valgt også at anvende de hændelsesrater for respons og remission, som er estimeret i protokollen, og som svarer til de rater, man ville forvente med komparator i en dansk kontekst. Ansøger har anvendt hændelsesrater fra studierne (komparatorarmen), men fagudvalget vurderer, at de er usædvanligt høje, hvilket tyder på en stor placeboeffekt eller effekt af komparatorregimet. Det kan blandt andet skyldes, at populationen er selekteret, som tidligere beskrevet, forventning om positiv effekt, en større grad af interaktion med sundhedspersonale, opstart af nyt antidepressiva samtidig med esketamin og ny administrationsform. Resultater med begge hændelsesrater præsenteres.

Vedvarende effekt 6 måneder
SUSTAIN-1: Langtidseffekterne af behandling måles, jf. protokollen ved 6 måneder. Fagudvalget vurderer, at resultaterne fra SUSTAIN-1 ikke direkte kan anvendes til at belyse, om der er længerevarende effekt af behandling med esketamin vs. placebo ved 6 måneder. Dette skyldes, at der ikke findes data for en reel komparatorgruppe (alle studiedeltagere, der randomiseres til placebo + OAD, har tidligere i studiet været i stabil remission/respons på esketamin), herudover er vedligeholdelsesfasen af varierende længde. Resultaterne fra SUSTAIN-1 gennemgås dog narrativt, da de kan informere om den fortsatte effekt af esketamin for dem som initialt responderer på esketamin og evt. relaps efter ophør med esketamin behandling.

Langtidseffekterne i SUSTAIN-1 vurderes med følgende forbehold:

- Selektionen af patienter forud for randomisering i SUSTAIN-1.
- Det efterspurgte effektmål er vedvarende remission eller respons i SUSTAIN-1, hvilket ikke defineres på samme måde som relaps. Tiden fra remission/respons til relaps er ofte en periode, hvor patienten får det tiltagende værre, og denne periode bør ikke medregnes som vedvarende remission/respons.

SUSTAIN-2 vs. TRD-kohorten

Ansøger har inkluderet en indirekte sammenligning af remission og response til tiden 6 måneder, hvor de sammenligner data fra SUSTAIN-2 med data fra det observationelle

studie TRD. SUSTAIN-2 er et *open-label* single-arm studie, hvor patienter får esketamin + ny OAD. TRD-kohorten er en observationel kohorte, hvor patienterne opstarter ny behandling herunder OAD og følges i 6 måneder. Der er ikke betydende forskelle i baselinekarakteristik mellem de to populationer.

Fagudvalget vurderer, at analysen af SUSTAIN-2 vs. TRD ikke kan anvendes til at vurdere den vedvarende effekt af esketamin + OAD vs. placebo + OAD. Fagudvalget ønsker ikke at inkludere analysen SUSTAIN-2 vs. TRD i denne vurdering, fordi der er betydende forskelle i studiedesignet og i sammenligningen af et klinisk studie med en observationel kohorte. Fagudvalget mener ikke, at sammenligningen er valid af følgende årsager:

I esketamin studierne ses store placeboeffekter, som fagudvalget vurderer ikke udelukkende skyldes opstart med ny OAD. Placeboeffekterne vurderes også at kunne skyldes forventning om ny effektiv behandling og mere interaktion med sundhedspersonale. En sammenligning mellem esketamin fra SUSTAIN-2 og et observationelt studie vil derfor overestimere effekten af esketamin, idet det ikke er muligt at justere for effekten af placebo.

I den observationelle TRD-kohorte følges patienterne mindre tæt end i det kliniske studie SUSTAIN-2, hvor patienterne følges ugentligt. Dette kan have stor betydning for både adhærens og den observerede effekt i studierne, idet fagudvalget forventer, at en tættere opfølgning vil have en positiv gevinst hos denne patientgruppe.

Response og remission er kun opgjort ved baseline og ved 6 måneder for TRD-kohorten. Det er derfor ikke muligt at undersøge, om den kortvarige effekt ved 4 uger af OAD i TRD-kohorten er tilsvarende OAD + placeboarmen i esketaminstudierne. Dette ville være nødvendigt for at kunne kvalificere, om en eventuel langtidseffekt ville være sammenlignelig.

I TRD-kohorten er der mindre opfølgning, og patienter kan frit skifte behandling eller lægge behandling oveni, efter aftale med lægen, uden at det ellers påvirker deres deltagelse i studiet eller opfølgning negativt. I esketaminstudierne kan patienter også skifte væk fra esketamin, men det betyder, at de udgår af studiet og mister muligheden for at få den nye behandling, som måske havde givet dem en bedring af symptomer eller en forhåbning om dette. Fagudvalget vurderer, at incitamentet for at ændre behandling er forskelligt i de to studier. Dette kan påvirke effekten af esketamin, når den sammenlignes med effekten af OAD fra TRD-kohorten, fordi det i analyserne anses for non-response, hvis patienten har skiftet behandling eller fået lagt ny behandling oveni frem til de 6 måneder.

På baggrund af ovenstående forhold vurderer fagudvalget, at data fra SUSTAIN-2 alene kan anvendes til at informere om den fortsatte effekt af esketamin for de patienter, som i induktionsperioden og vedligeholdelsesfasen responderer på esketamin - uden brug af komparatorgruppe. Herudover kan SUSTAIN-2 informere om sikkerheden ved esketaminbehandling. Fagudvalget præsenterer og vurderer ikke data for TRD-kohorten yderligere i rapporten.

5.2.1 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen, som inkluderer TRANFORM-1, -2 og 3. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (Bilag 2).

Effekt opgjort ved uge 4: Der er nedgraderet for risk og bias grundet mangelfuld blinding. Der er nedgraderet for indirekthed, fordi populationerne er selekterede.

Effekt opgjort ved 6 måneder: Der findes ikke analyser, som vurderes at være valide, og evidensens kvalitet er derfor meget lav

Samlet set er evidensens kvalitet meget lav.

5.2.2 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1

Effektmål	Vigtighed	Måleenhed (mindste klinisk relevante forskel)	Tidshorisont	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
				Forskel (95% CI)	Foreløbig værdi	Forskel (95% CI)	Foreløbig værdi	
Remission	Kritisk	Andel der reducerer score til ≤ 11 point på MADRS (15 %-point), NNT=7	4 uger	7,0 %-point [1,4; 14,56], NNT=14	Ingen dokumenteret merværdi	1,50 [1,10; 2,04]	Merværdi af ukendt størrelse	Kan ikke kategoriseres
			6 mdr.	-	Kan ikke kategoriseres	-	Kan ikke kategoriseres	
Respons	Vigtig	Andel der reducerer MADRS score fra baseline med 50 % (20 %-point), NNT=5	4 uger	7,6 %-point [3,2; 12,6], NNT=13	Ingen dokumenteret merværdi	1,38 [1,16; 1,63]	Moderat merværdi	Kan ikke kategoriseres
			6 mdr.	-	Kan ikke kategoriseres	-	Kan ikke kategoriseres	
Livskvalitet	Vigtig	Gennemsnitlig ændring fra baseline på EQ-5D (index score) (0,07 point)	4 uger	0,06 point [0,01; 0,10]	Ingen dokumenteret merværdi	-	-	Kan ikke kategoriseres
			6 mdr.	-	Kan ikke kategoriseres	-	-	
Uønskede hændelser	Kritisk	Andel der oplever alvorlige uønskede hændelser (SAE'er) (5 %-point)	4 uger	0,4 %-point [-0,63; 4,29]	Kan ikke kategoriseres	1,40 [0,37; 5,29]	Kan ikke kategoriseres	Kan ikke kategoriseres
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
		Andel der ophører behandling (20 %-point)	4 uger	2,72 %-point [-0,051; 10,183]	Kan ikke kategoriseres	2,60 [0,97; 6,99]	Kan ikke kategoriseres	Kan ikke kategoriseres
			6 mdr.	Narrativ gennemgang	Kan ikke kategoriseres	Narrativ gennemgang	Kan ikke kategoriseres	
Konklusion: Esketamin i kombination SSRI eller SNRI kan have en gavnlig effekt for en mindre andel af patienter. For nogle patienter kan effekten vare ved i ≥ 6 måneder. Samtidig har esketamin betydende bivirkninger, som gør, at Medicinrådet ikke finder det klinisk relevant at anvende esketamin efter svigt på blot to tidligere antidepressiva.								
Samlet kategori for lægemidlets værdi			Kan ikke kategoriseres					
Kvalitet af den samlede evidens			Meget lav					

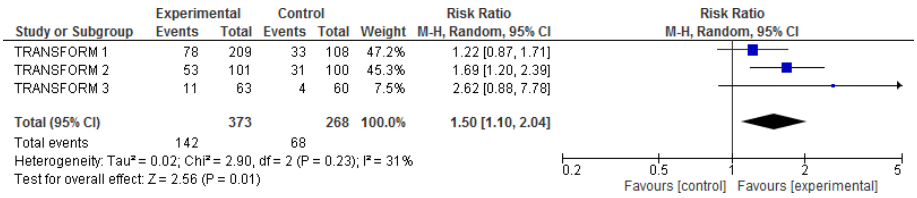
CI = konfidensinterval, NNT= numbers needed to treat

5.2.3 Kortidseffekt (4 uger)

Afsnittets data og konklusioner er overordnet set uændrede i forhold til den oprindelige vurderingsrapport.

Remission (kritisk)
Effektmålet remission ønskes opgjort som andel, der reducerer scoren til ≤ 11 point på MADRS (mindste klinisk relevante forskel: 15 %-point). *Cut-off* for remission i studierne er en MADRAS score ≤ 12. Fagudvalget vurderer, at denne forskel i *cut-off* ikke vil påvirke effektestimaterne væsentligt.

Måletidspunkt 4 uger, remission
Resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter, der opnår remission på tværs af de tre studier, er 38 % (142/373) hos patienter, der modtog esketaminbehandling, sammenlignet med 25 % (68/268) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på RR 1,50 [1,10; 2,04] til fordel for esketamin (Figur 1).



Figur 1. Remission. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin

Baseret på den *relative effektforskel* kategoriseres esketamin foreløbigt med merværdi af ukendt størrelse vedr. remission efter 4 ugers behandling.

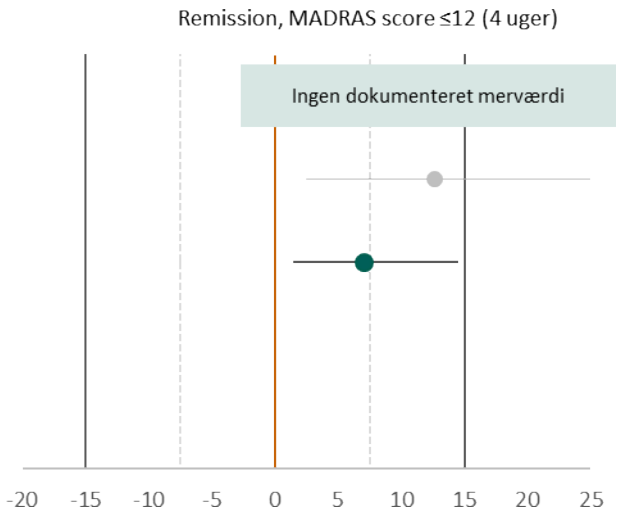
Ansøger har indsendt data for "*observed cases*" fremfor ITT-populationen. Det vil sige, at *missing* data ikke er imputeret, hvilket også er beskrevet i Medicinrådets metodevejledning. Denne fremgangsmåde kan dog i nogle tilfælde føre til en uhensigtsmæssig favorisering af behandlingsarme med mest *missing* data; i dette tilfælde interventionsarmen. Hvad angår effektmålet remission vurderer fagudvalget, at det er relevant med en sensitivitetsanalyse, hvor man antager, at patienter som af forskellige årsager er udgået af studiet, ikke er i fuld remission. I sensitivitetsanalysen er der observeret tilsvarende resultat som i hovedanalysen (RR = 1,44 [1,05; 1,97]).

Remissionsraten for den danske population med behandlingsresistent depression for komparator er i protokollen sat til at være 14 %. Ved beregning via den relative forskel på RR 1,50 [1,10; 2,04] bliver den absolutte effektforskel 7,0 %-point [1,4; 14,56] (NNT=14).

Ansøger har anvendt en hændelsesrate baseret på remissionsraterne i TRANSFORM-studierne. Fagudvalget vurderer, at remissionsraterne er bemærkelsesværdig høje. Til sammenligning, hvis man anvender remissionsraten fra studierne på 25,4 %, er den absolutte effektforskel 12,7 %-point [2,5; 26,4] til fordel for esketamin.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af esketamin *ingen dokumenteret merværdi* vedr. remission ved 4 uger.

Den absolutte forskel er afbildet i Figur 2 nedenfor.



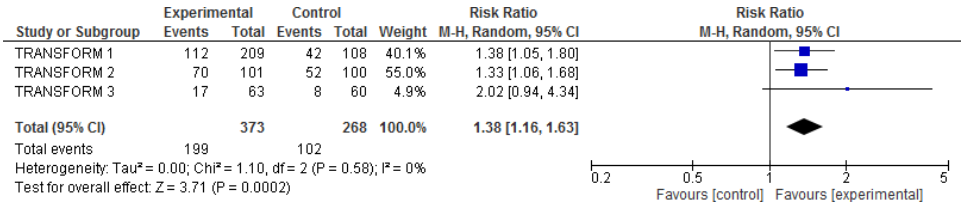
Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for remission ved 4 uger. Det grønne estimat angiver effektforskellen baseret på hændelsesraten i protokollen, mens det grå estimat angiver effektforskellen baseret på hændelsesraten fra studierne. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Respons (vigtig)

Jævnfør protokollen ønskes effektmålet respons opgjort som andel, der reducerer MADRS scoren til ≥ 50 % fra baseline (mindste klinisk relevante forskel: 20 %-point).

Måletidspunkt 4 uger, respons

Resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter, der opnår et respons på tværs af de tre studier, er 53 % (199/373) hos patienter, der modtog esketamin, sammenlignet med 38 % (102/268) hos patienter, der modtog placebo og heraf en beregnet relativ forskel på RR 1,38 [1,16; 1,63] til fordel for esketamin (Figur 3).



Figur 3. Respons. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin

Baseret på den relative effektforskel kategoriseres esketamin foreløbigt med moderat merværdi vedr. respons efter 4 ugers behandling.

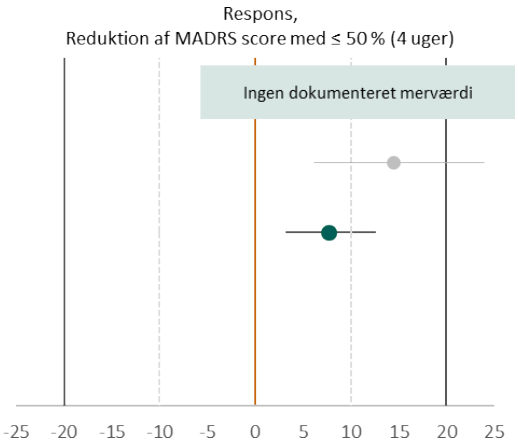
Ansøger har indsendt data for "*observed cases*" fremfor ITT-populationen. Det vil sige, at *missing* data ikke er imputeret, hvilket også er beskrevet i Medicinrådets metodevejledning. Denne fremgangsmåde kan dog i nogle tilfælde føre til en uhensigtsmæssig favorisering af behandlingsarme med mest *missing* data; i dette tilfælde interventionsarmen. Hvad angår effektmålet respons, vurderer fagudvalget, at det er relevant med en sensitivitetsanalyse, hvor man antager, at patienter, som af forskellige årsager er udgået af studiet, ikke er i respons. I sensitivitetsanalysen er der observeret samme resultat som i hovedanalysen (RR = 1,36 [1,14; 1,62]).

Responsraten for den danske population med behandlingsresistent depression for komparator er i protokollen sat til at være 20 %. Ved anvendelse af responsrate på 20 % er den absolutte effekt 7,6 %-point [3,2; 12,6].

Ansøger har anvendt en hændelsesrate baseret på responsraterne i studierne. Fagudvalget vurderer, at responsraterne er bemærkelsesværdig høje. Til sammenligning, hvis man anvender responsraten fra studierne på 38,1 %, er den absolutte effektforskel 14,5 %-point [6,1; 24,0] til fordel for esketamin.

Punktestimatet for den absolutte effektforskel (7,6 %-point [3,2; 12,6]) afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af esketamin ingen dokumenteret merværdi vedr. respons ved 4 uger.

Den absolutte forskel er afbildet i Figur 4 nedenfor.



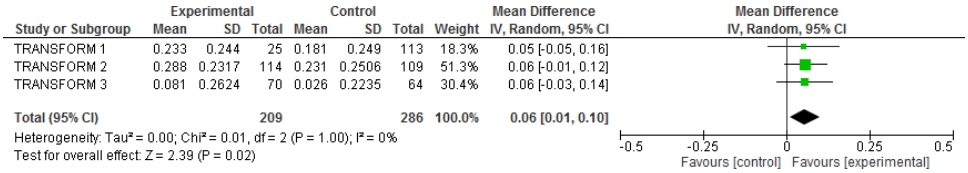
Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for respons ved 4 uger. Det grønne estimat angiver effektforskellen baseret på hændelsesraten i protokollen, mens det grå estimat angiver effektforskellen baseret på hændelsesraten fra studierne. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Livskvalitet (vigtigt)

Jævnfør protokollen ønskes effektmålet *livskvalitet* opgjort som den gennemsnitlig ændring fra baseline på EQ-5D (mindste klinisk relevante forskel: 0,07 point).

Måletidspunkt 4 uger, livskvalitet

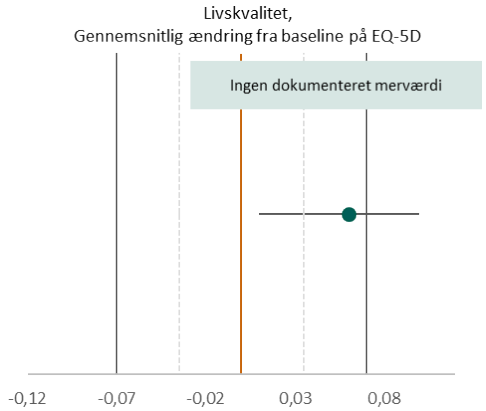
Der er leveret data fra de 3 TRANSFORM-studier. Hændelsesraten til beregning af den absolutte forskel er hentet fra studierne. Resultatet fra metaanalysen efter 4 ugers behandling viser, på tværs af de tre studier, en absolut forskel på 0,06 [0,01; 0,10] til fordel for esketeminbehandlingen, se Figur 5 nedenfor.



Figur 5. Livskvalitet. Forest plot over absolutte forskelle (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel (Figur 6). Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Samtidig inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af esketamin ingen dokumenteret merværdi vedr. livskvalitet ved 4 uger.

Den absolutte forskel er afbildet i Figur 6 nedenfor.



Figur 6. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (EQ-5D index score) ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

5.2.4 Vedvarende effekt

Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Fagudvalget vurderer, at data fra SUSTAIN 1 og SUSTAIN 2 kan bruges til at informere om den vedvarende effekt af esketamin for de patienter, som initielt responderer på esketamin. Fagudvalget vurderer, at der ikke findes data, som kan fungere som en valid komparatorgruppe. Data fra SUSTAIN-1 og 2 gennemgås deskriptivt.

Måletidspunkt 6 måneder, remission
SUSTAIN-1: I SUSTAIN 1 er remission og respons opgjort som samlet ved 16 uger. Data gennemgås derfor samlet under effektmålet respons nedenfor.

SUSTAIN-2: Ansøger har indsendt data for patienter, som indtrådte direkte i SUSTAIN-2. Remission er opgjort ved MADRS ≤ 10.

Ansøger opgør data på flere måder, hvor der er forskel på håndteringen af missing data. I opgørelserne er det mellem 28-32 %, der opnår remission med esketamin + OAD efter 26 uger.

Ved den opgørelse, som Medicinrådet finder mest anvendelig, er der 204/669 = 30 % som er i remission efter induktionsfasen på 4 uger. Efter 26 uger er der 176/549 = 32 % patienter, som er i remission. Disse patienter kan både være de samme som opnåede remission ved 4 uger, men kan også være patienter, som opnåede respons ved 4 uger og efterfølgende opnår remission.

Måletidspunkt 6 måneder, respons
SUSTAIN-1: I SUSTAIN-1 er remission og respons opgjort som samlet ved 16 uger. Data gennemgås derfor samlet nedenfor.

SUSTAIN-2: Respons er opgjort som > 50 % reduktion i MADRS.

Ansøger opgør data på flere måder, hvor der er forskel på håndteringen af missing data.

I opgørelserne er det mellem 41,5-46,8 %, der opnår respons med esketamin + OAD efter 26 uger.

Ved den opgørelse, som Medicinrådet finder mest anvendelig, er der 525/669 = 78 %, som har opnået et respons efter induktionsfasen på 4 uger. Efter 26 uger er der 259/549 = 46,6 % af patienter, som fortsat har respons.

Gennemgang af resultater fra SUSTAIN-1: Remission, respons og relaps ved 16 uger
Gennemgangen af SUSTAIN-1 er uændret fra den oprindelige vurderingsrapport.

SUSTAIN-1 er et relapsstudie, som måler på tid til relaps ved fortsat behandling med esketamin + OAD eller skift til placebo + OAD efter 16 ugers behandling (4 ugers induktion og 12 ugers optimering). Der kan i dette studie ligeledes findes information omkring, hvor stor en andel af patienterne, som er i stabil remission (defineret som total MADRS ≤ 12 i 3 ud af 4 uger af optimeringsfasen) eller har stabilt respons (defineret som ≥ 50 % reduktion i total MADRS score fra baseline i de sidste to uger af optimeringsfasen) efter en 16 ugers introduktion- og optimeringsfase. Relaps i studierne defineres som total MADRS score ≥ 22 ved to konsekutive målinger, adskilt med 5-15 dage og/eller hospitalisering for forværring i depressive symptomer eller enhver anden klinisk relevant begivenhed, der indikerer relaps af depressiv sygdom såsom selvmordsforsøg eller fuldbyrdet selvmord eller hospitalisering som følge af selvmordsforebyggelse. Tidshorisonten for den enkelte patient er tid fra randomisering til det første relaps i vedligeholdelsesfasen (op til 92 uger). Herunder ses en kvalitativ gennemgang af resultaterne for SUSTAIN-1, der omfatter effektmålene remission og respons.

Overførte patienter til SUSTAIN-1 fra TRANSFORM-1:

- Esketamin-behandlede patienter:
  - 78/233 patienter var i remission efter 4 uger. 112/233 havde respons efter 4 uger (48 %).
  - Efter 16 uger er der 46 stabile remittere (20 %). Efter 16 uger var der 25 stabile respondere (11 %).
  - 112 overføres til SUSTAIN-1 (46 + 25)/112 = 63 % bevarer et respons.

- Placebo:
  - 33/113 var i remission efter 4 uger. 42/113 havde respons efter 4 uger (37 %).
  - Efter 16 uger var der samlet 22/113 i stabil remission eller respons (19 %).
  - 38 overføres til SUSTAIN-1 22/3 = 58 % bevarer et respons.

Overførte patienter til SUSTAIN-1 fra TRANSFORM 2:

- Esketamin-behandlede patienter:
  - 53/116 patienter var i remission efter 4 uger. 70/116 havde respons efter 4 uger (60 %).
  - Efter 16 uger er der 20 stabile remittere (17 %). Efter 16 uger var der 26 stabile respondere (22 %).
  - 70 overføres til SUSTAIN-1 (20 + 26)/70 = 66 % bevarer et respons.

- Placebo:
  - 31/111 var i remission efter 4 uger. 52/111 havde respons efter 4 uger (47 %).

- Efter 16 uger var der samlet 33/111 i stabil remission eller respons (30 %).
- 48 overføres til SUSTAIN-1 33/48 = 69 % bevarer et respons.

SUSTAIN-1 direkte indtræden:

- Esketamin-behandlede patienter:
  - 273/437 havde respons efter 4 uger (62 %).
  - Efter 16 uger er der 110 stabile remittere (25 %). Efter 16 uger var der 73 stabile respondere (17 %).
  - 273 fortsætter i SUSTAIN-1 (110 + 73)/273 = 67 % bevarer et respons.

Optimeringsfase 4-16 uger

I alle 3 studier (TRANSFORM-1, -2 og SUSTAIN-1 direkte indtræden) var der hhv. 48 %, 60 % og 62 %, der fik et respons på esketamin ved 4 uger. Af patienter, som blev behandlet med esketamin, og som fik et respons ved 4 uger, var der forsat et respons for 63-67 % af patienterne ved 16 uger.

Der var i TRANSFORM-1 og -2 færre patienter i placeboarmene (37 % og 47 %), der fik respons til tiden 4 uger i forhold til esketaminarmene (48 % og 60 %). Af patienter, som fik placebo, og som fik et respons ved 4 uger, var der fortsat en effekt for hhv. 58 % og 69 % af patienterne i TRANSFORM-1 og -2 ved 16 uger.

Dermed kan man se, at der fortsat er flere patienter, som har respons med esketaminbehandling end ved placebo ved 16 uger, og at der stadig er et respons for 63-67 % af patienterne ved uge 16. Samtidig kan det dog ses, at hvis man har opnået en effekt ved 4 ugers placebobehandling, er der fortsat respons for en tilsvarende andel ved 16 uger (58-69 %). Ved sammenligning af esketamin overfor placebo fra 4 til 16 uger ses altså en vedvarende effekt, som er i omtrentlig samme relative størrelsesorden, som observeres ved 4 uger. Dette tyder på, at der ikke er nogen mereffekt af esketamin overfor placebo fra 4 til 16 uger.

Vedligeholdelsesfase

I vedligeholdelsesfasen randomiseres patienter i stabil remission eller stabilt respons til at fortsætte esketamin eller overgå til placebo, og det primære endemål er tid til relaps. Både for patienter i stabil remission eller i stabilt respons ses flere tilfælde af relaps hos patienter, som stopper esketaminbehandling. For patienter i behandling med esketamin, der opnåede stabil remission, ses, at 16 patienter (25,8 %) oplevede relaps, hvor 34 patienter (57,6 %) af de patienter der blev randomiseret til placebo + OAD efter esketamin oplevede et relaps (HR: 0,49; 95 % CI: 0,29;0,84). For patienter i behandling med esketamin der opnåede stabil respons ses, at 24 patienter (26,7 %) oplevede relaps, hvor 39 patienter (45,3 %) af de patienter, der blev randomiseret til placebo + OAD efter esketamin, oplevede et relaps (HR: 0,30; 95 % CI: 0,16; 0,55).

Den vedvarende effekt af esketamin kunne ifølge fagudvalget bedre have været belyst, hvis ansøger havde fortsat TRANSFORM-studierne i længere tid og med opfølgning efter endt behandling. Sådanne studier ville også have kunne belyse omfanget af alvorlige uønskede hændelser efter længerevarende brug af esketamin, misbrugspotentialet og eventuelle forventelige udfordringer med seponering i relation til en ægte placebogruppe. Fagudvalget mener, at observationelle data for effekter af esketamin

uden en placebokontrol kan være særligt skævvridende, da de høje hændelsesrater i kontrolgrupperne fra TRANSFORM-1, -2 og -3 og SUSTAIN-1 indikerer placebo- og noceboeffekter af behandling.

Vurdering af vedvarende effekt ved uge 16 (SUSTAIN-1)
Fagudvalget vurderer, at data ved 16 uger støtter konklusionen for data ved 4 uger. Data viser, at der hos patienter, der opnår respons med esketamin ved 4 uger, er et vedvarende respons ved uge 16 for ca. 2/3 af patienterne. Denne andel er tilsvarende den andel, der har vedvarende respons fra uge 4-16 i placeboarmen. Der ses altså ikke en yderligere mereffekt af esketamin fra uge 4-16 hos patienter, som har oplevet remission eller respons i studiernes induktionsfase (op til uge 4) og heller ikke et øget tilbagefald. Data kan ikke opdeles i stabil remission og stabilt respons, da disse data ikke er opgjort separat for placeboarmen. Fagudvalget vurderer, at relapsraten er relativ høj i esketamingruppen og mener ikke, at behandlingen bør seponeres efter 16 uger hos patienter, der har opnået stabilt respons eller stabil remission med esketaminbehandling, idet der vil være større risiko for at få et tilbagefald. Fagudvalget kan på foreliggende datagrundlag ikke vurdere, hvornår behandling med esketaminkan forsøges seponeret.

Samlet vurdering af effektmålet remission
Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategoriseres** efter Medicinrådets metoder vedr. remission, da den længerevarende effekt ikke er tilstrækkeligt belyst, samt at populationerne adskiller sig i en grad, der medfører usikkerhed om, hvorvidt de rapporterede estimater kan overføres til danske patienter.

Fagudvalget vurderer, at den absolutte forskel i remissionsraterne ved 4 uger har værdi for patienter med behandlingsresistent depression, selvom effekten er mindre end den mindste klinisk relevanteforskel på 15 %-point. Fagudvalget lægger især vægt på, at remission er svært at opnå hos patienter med behandlingsresistent depression, der lever med en alvorlig, livsforringende kronisk sygdom uden mange behandlingsmuligheder.

Data på den længerevarende effekt er sparsom, da der ikke findes tilstrækkelig komparativt data. Data fra esketaminstudier viser, at hos andelen af de patienter, som opnår remission ved 4 uger, er effekten vedvarende i op til 6 måneder. Fagudvalget vurderer, at det er positivt, at omkring 30 % opnår remission i op til 6 måneder. Der mangler dog sammenligning med en repræsentativ komparatorgruppe, som også tager højde for effekten af komparator inkl. placeboeffekten.

Samlet vurdering af effektmålet respons
Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategoriseres** efter Medicinrådets metoder vedr. respons, idet den længerevarende effekt ikke er tilstrækkeligt belyst, samt at populationerne adskiller sig i en grad, der medfører usikkerhed om, hvorvidt de rapporterede estimater kan overføres til danske patienter.

Fagudvalget vurderer, at den absolutte forskel på 7,6 %-point svarende til NNT på 13 i responsraterne ved 4 uger ikke er klinisk relevant. Fagudvalget lægger i den vurdering især vægt på, at behandlingsrespons sjældnere er et udtryk for en blivende effekt hos patienter med behandlingsresistent depression.

Data på den længerevarende effekt er sparsom, da der ikke findes tilstrækkelig komparativt data. Data fra esketaminstudierne viser, at hos en andel af patienterne, som opnår respons, er effekten vedvarende i op til 6 måneder. Fagudvalget vurderer, at det er positivt, at omkring 45 % opnår respons i op til 6 måneder. Der mangler dog sammenligning med en repræsentativ komparatorgruppe, som også tager højde for effekten af komparator inkl. placeboeffekten.

Måletidspunkt 6 måneder, livskvalitet
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Data fra SUSTAIN-1 anvendes ikke, da livskvalitet i SUSTAIN-1 er målt som ændring fra baseline i vedligeholdelsesfasen til det tidspunkt, hvor den enkelte patient afslutter studiet. Tidsperioden fra baseline til afslutning kan være forskellig fra patient til patient og kan være defineret af tilbagefald, studieafslutning eller ophør af andre årsager. Fagudvalget vurderer derfor (som EMA), at dette livskvalitetsdata ikke bør indgå i vurderingen, da det usikkert, og at der er risiko for introduktion af bias ved at have forskellige måletidspunkter, hvoraf nogle er influeret af sygdomstilbagefald. Herudover er livskvalitets data ikke tilgængelig fra SUSTAIN-3. Det vil derfor kun være data fra SUSTAIN-2, som gennemgås narrativt i det følgende.

SUSTAIN-2, som kun inkluderede esketamin-behandlede patienter, viser en gennemsnitlig stigning i livskvaliteten fra baseline til afslutningen af induktionsfase efter 4 uger på 0,190 point på EQ-5D-5L (SD: 0,21; n = 745). Der ses herefter ingen ændring fra baseline ved start af optimerings- og vedligeholdelsesfasen på 48 uger til slutningen af denne fase på -0,009 (SD: 0,14; n=603).

Samlet vurdering af effektmålet livskvalitet
Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategoriseres** efter Medicinrådets metoder vedr. livskvalitet, idet den længerevarende effekt ikke er tilstrækkeligt belyst i sammenhæng med relevant komparator. Ved 4 uger har esketamin ingen dokumenteret merværdi vedr. livskvalitet sammenlignet med komparator.

5.2.5 Gennemgang af bivirkning og sikkerhedsdata

Sikkerhedsprofilen er gennemgået på ny, og data fra 4 uger er uændret fra sidste vurdering.

Uønskede hændelser (kritisk)
Data fra 4 uger er uændret fra den oprindelige vurderingsrapport.

Som beskrevet i protokollen er effektmålet uønsket hændelser kritisk for vurderingen af lægemidlets værdi for patienterne, fordi de har stor betydning for den enkelte patients livskvalitet. Det vurderes dog, at der må accepteres et vist niveau af behandlingsophør, hvis den andel af patienter, som forbliver i behandling, oplever en relevant bedring.

Effektmålet ønskes belyst på 3 måder:

1. Andel, der oplever alvorlige uønskede hændelser (SAE) (mindste klinisk relevante forskel: 5 %-point)
2. Andel, der ophører behandling (mindste klinisk relevante forskel: 20 %-point) inkl. information om specifikke årsager hertil
3. En kvalitativ gennemgang af uønskede hændelser og død uanset årsag.

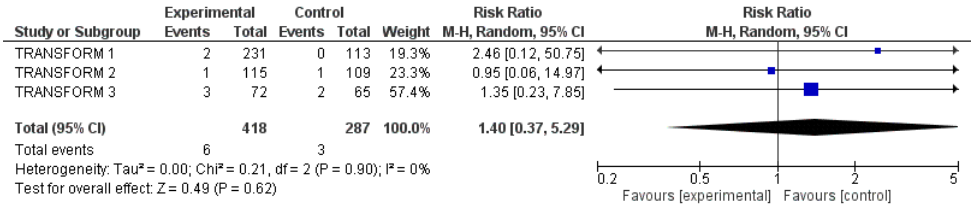
Gennemgangen tager udgangspunkt i publicerede studier, produktresumé og EPAR med henblik på at vurdere, om der er forskel mellem grupperne mht. alvorlighed, håndterbarhed og hyppighed af uønskede hændelser og død uanset årsag. Data-on-file fra ATU-kohorten og SUSTAIN-3 vil også blive anvendt i den kvalitative gennemgang af sikkerheden og bivirkninger ved brug af esketamin.

Måletidspunkt 4 uger, alvorlige uønskede hændelser
Det samlede resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter med alvorlige uønskede hændelser (SAE) er 1,4 % (6/418) hos patienter, der modtog esketamin + OAD sammenlignet med 1,0 % (3/287) hos patienter, der modtog placebo + OAD og heraf er beregnet en relativ forskel på 1,40 [0,37: 5,29], se Figur 7.

Baseret på den relative effektforskel, som også fremgår af Tabel 3, kan esketamin foreløbigt ikke kategoriseres vedr. alvorlige uønskede hændelser.

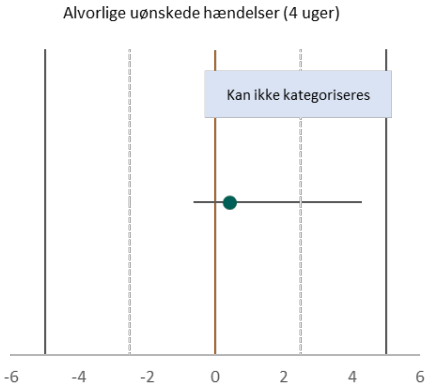
Der er ikke påvist en klinisk relevant forskel mellem esketamin og placebo for effektmålet uønskede hændelser, da få hændelser bevirker, at konfidensintervallet er bredt og indeholder værdier, som kan føre til forskellige konklusioner, hvorfor den kliniske værdi på den relative skala ikke kan kategoriseres.

Figur 7. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin. Alvorlige uønskede hændelser.



Med en samlet hændelsesrate i placebogruppen på 1,0 % beregnes den absolutte forskel til 0,4 %-point [-0,63; 4,29] flere SAE's i esketamin-gruppen. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0. Derfor kan den foreløbige værdi af esketamin vedr. andel, der oplever alvorlige uønskede hændelser, ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet på Figur 8 nedenfor.



Figur 8. Punktestimat og 95 % konfidensinterval for den absolutte forskel for alvorlige uønskede hændelser ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier, svarende til halvdelen af den mindste klinisk relevante forskel.

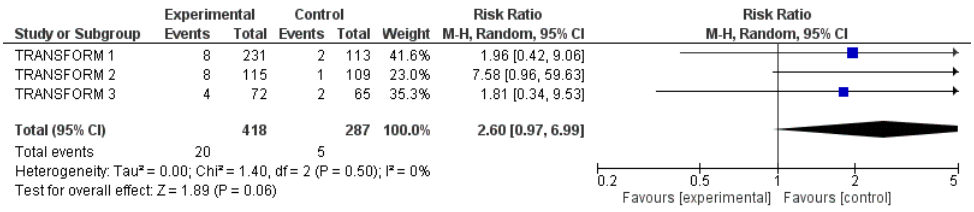
Fagudvalget vurderer ud fra ovenstående beregninger og de meget små hændelsesrater, at der ikke er betydende klinisk forskel mellem esketamin og placebo for andel af patienter, der oplever en SAE indenfor 4-ugers behandling.

Måletidspunkt 6 måneder, alvorlige uønskede hændelser
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin på effektmålet alvorlige uønskede hændelser ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres efter Medicinrådets metoder ved 6 måneder. Fagudvalget lægger vægt på den kvalitative gennemgang for vurdering af hændelser og bivirkninger.

Måletidspunkt 4 uger, behandlingsophør grundet uønskede hændelser
Det samlede resultat fra metaanalysen efter 4 ugers behandling viser, at andelen af patienter med behandlingsophør er 4,8 % (20/418) hos patienter, der modtog esketamin + OAD sammenlignet med 1,7 % (5/287) hos patienter, der modtog placebo + OAD og heraf en beregnet relativ forskel på 2,60 [0,97: 6,99], se Figur 9.

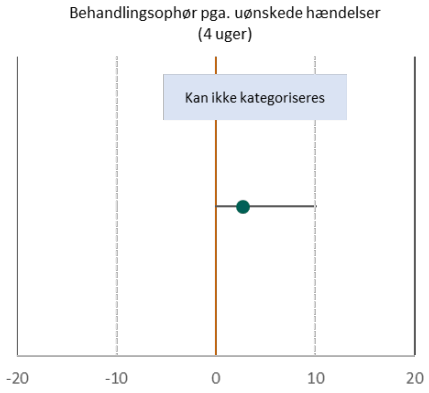
Baseret på den relative effektforskel, som også fremgår af Tabel 3, kan esketamin foreløbigt ikke kategoriseres vedr. behandlingsophør. Der er ikke påvist en forskel mellem esketamin og placebo. Pga. få hændelser er konfidensintervallet bredt og indeholder værdier, som kan føre til forskellige konklusioner, hvorfor den kliniske værdi på den relative skala ikke kan kategoriseres.

Figur 9. Forest plot over relativ risiko (RevMan version 5.3) af TRANSFORM-1, -2, og -3 efter 4 ugers behandling med esketamin. Behandlingsophør grundet uønskede hændelser.



Med en samlet hændelsesrate i placebogruppen på 1,7 % beregnes den absolutte forskel til 2,72 %-point [- 0,051; 10,183]. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af esketamin vedr. behandlingsophør ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i Figur 10 nedenfor.



Figur 10. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet uønskede hændelser ved 4 uger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Fagudvalget vurderer ud fra ovenstående beregninger, at der indenfor 4 ugers behandling formentlig er flere patienter, som ophører behandling med esketamin i forhold til placebo. Forskellen er dog i en størrelsesorden, der ikke er klinisk relevant.

Måletidspunkt 6 måneder, behandlingsophør grundet uønskede hændelser
Der findes ikke tilstrækkeligt kvantitativt data, som kan bruges til kategorisering af esketamin ved 6 måneder. Derfor kan værdien af esketamin ikke kategoriseres ved 6 måneder. Fagudvalget lægger vægt på den kvalitative gennemgang for vurdering af hændelser og bivirkninger.

Kvalitativ gennemgang af alvorlige uønskede hændelser, behandlingsophør, død uanset årsag og bivirkninger, alle måletidspunkter

Fagudvalget har i forbindelse med denne revurdering genbesøgt den kvalitative gennemgang af sikkerheden ved esketamin.

Alvorlige uønskede hændelser (SAE)
Ansøger opgør *serious treatment emergent adverse events* (TEAE's) som SAE. Der er i de inkluderede studier registreret følgende SAE udover død (død uanset årsag gennemgås i det følgende).

I TRANSFORM-1 oplevede 2 af de 231 studiedeltagere (0,87 %) i esketaminbehandling én eller flere SAE. Én studiedeltager i esketamin-gruppen oplevede forværring i depression, og én deltager oplevede hovedpine. Begge SAE blev vurderet til muligvis at være relateret til esketaminbehandlingen.

I TRANSFORM-2 oplevede ingen i esketaminbehandling en SAE (udover ét dødsfald som beskrives i det følgende). I placebogruppen oplevede 1 af 109 studiedeltagere (0,9 %) én eller flere SAE. Denne SAE blev vurderet til ikke til at være relateret til placebo-behandlingen.

I TRANSFORM-3 oplevede 3 af de 72 studiedeltagere (4,2 %) i esketaminbehandling én eller flere SAE. Én studiedeltager oplevede angst, én oplevede forhøjet blodtryk og én pådrog sig en hoftefraktur. De to første SAE blev vurderet til muligvis at være relateret til esketaminbehandlingen. I placebogruppen oplevede 2 af de 65 studiedeltagere én eller flere SAE (3,1 %). Én studiedeltager oplevede gangforstyrrelse og én oplevede svimmelhed. Gangforstyrrelsen blevet vurderet til muligvis at være relateret til OAD-behandlingen.

I SUSTAIN-1 oplevede 13 af de 437 studiedeltagere (3 %) i introduktionsfasen, 11 af de 455 studiedeltagere i optimeringsfasen (2,4 %) og 4 af de 152 studiedeltagere i vedligeholdelsesfasen (2,6 %) én eller flere SAE i esketamin-gruppen. 6 af dem som opstod i introduktionsfasen blev vurderet til muligvis at være relateret til esketaminbehandlingen (ubalance i det autonome nervesystem, disorientering, hypotermi, lacunar slagtilfælde, sedering, *simple partial seizure*s og selvmordstanker). Én af de 145 studiedeltagere (0,7 %) i placebogruppen oplevede én eller flere SAE i vedligeholdelsesfasen.

I SUSTAIN-2 oplevede 55 af de 802 studiedeltagere (6,9 %) i esketaminbehandling én eller flere SAE. De typiske SAE var: depression (n = 8), selvmordstanker (n = 6), selvmordsforsøg (n = 6), angst (n = 2) og gastroenteritis (n = 2). 4 af disse (0,5 %) blev vurderet til muligvis at være relateret til esketaminbehandlingen. Disse var delirium, angst + vrangforestillinger, selvmordstanker og selvmordsforsøg.

[redacted]

[redacted]

[redacted]

Behandlingsophør grundet uønskede hændelser
Behandlingsophør som følge af TEAE'er ses hyppigere i esketamingruppen vs. placebogruppen i TRANSFORM-1, -2 og -3 (4,6 % vs. 1,4 % i TRANSFORM-1 og -2; 5,6 % vs. 3,1 % i TRANSFORM-3). Behandlingsophør som følge af TEAE'er i SUSTAIN-1 var som følger: Induktionsfasen: 22/437 (5 %) patienter i esketamingruppen (direkte indtrådte patienter); optimeringsfasen: 5/455 (1,1 %) patienter i esketamingruppen (direkte indtrådte + overførte patienter); vedligeholdelsesfasen: 4/152 (2,6 %) patienter i esketamingruppen vs. 3/145 (2,1 %) patienter som blev randomiseret til placebo (direkte indtrådte patienter + overførte patienter). Ifølge SUSTAIN-2 er den overordnede rate for behandlingsophør efter op til et års behandling med esketamin 9,5 % [redacted] I SYNAPSE-studiet ophører 5 % af esketaminbehandlede patienter, grundet AEs i den dobbeltblindend fase, mens 2 % ophører grundet AEs i open-label fasen. [redacted]

De typiske TEAE'er, der ligger til grund for behandlingsopgør, er, på tværs af fase 3-studierne og nævnt i rækkefølge af hyppighed: angst, depression, forhøjet blodtryk, svimmelhed, *suicidal ideation*, dissociation og kvalme.

Død uanset årsag
I alt 4 dødsfald er registreret på tværs af de afsluttede fase-2 og fase-3 studier, hvori 1708 studiedeltagere blev behandlet med esketamin (0,2 %). Ingen dødsfald er registreret for placebogruppen, hvori der indgik 486 studiedeltagere [25]. Det bør bemærkes, at observationstiden for patienter, der behandles med placebo, er markant kortere, end for patienter der behandles med esketamin, hvorfor disse resultater ikke bør sammenlignes én til én. Herudover er der rapporteret [redacted] i det igangværende SUSTAIN-3 fase 3-studie (n = 1093).

I fase 2-studiet SYNAPS blev der rapporteret ét dødsfald. Her døde en 41-årig mand af selvmord 45 dage inde i studiet og 20 dage efter sidste dosisadministration af esketamin. Dette dødsfald blev ikke vurderet til at være relateret til esketaminbehandlingen. I fase 3-studiet TRANSFORM-2 blev ét dødsfald rapporteret i esketamin-gruppen. Her døde en 41-årig mand som følge af en færdselsulykke ca. 28 timer efter sidste dosisadministration af esketamin (84 mg, dag 16). Ingen tidligere selvmordtanker eller -forsøg var registreret for patienten, som herudover heller ikke havde oplevet uønskede hændelser forud for færdselsulykken. Dette dødsfald blev ikke vurderet til at være relateret til esketaminbehandlingen.

I fase 3-studiet SUSTAIN-2 blev to dødsfald rapporteret. Her døde én 60-årig mand med akut respiratorisk svigt og akut hjertesvigt 113 dage inde i studiet. Herudover døde én

55-årig kvinde af selvmord 188 dage inde i studiet og 12 dage efter sidste dosisadministration af esketamin. Disse dødsfald blev vurderet til muligvis at være relateret til esketaminbehandlingen.

[redacted]

Bivirkninger
De hyppigst forekommende *Adverse Drug Reactions* (bivirkninger) i fase 3-studierne inkluderer svimmelhed, dissociation, kvalme, hovedpine, somnolens, smagsforstyrrelser, vertigo, hypæstesi, opkastning og forhøjet blodtryk [13,20–22]. EPAR angiver, at hovedparten af de uønskede hændelser er milde til moderate, og at de fleste *severe TEAEs* ophører inden for et døgn (88,9 % i esketamin-grupperne og 83,3 % i placebogrupperne sammenlagt for TRANSFORM-1 og -2). Bivirkninger til behandling med esketamin knytter sig primært til symptomer relateret til nervesystemet (64,1 %), psykiatriske symptomer (46,1 %) og mave-tarm-symptomer (32,2 %) [25].

Beskrivelse af udvalgte hændelser

Selvmordstanker
Selvmordstanker er målt med C-SSRS *(Columbia-Suicide Severity Rating Scale*). I TRANSFORM-studierne er *suicidal ideation* ved baseline rapporteret hos 17,1 % til 25,3 % i esketamingruppen og 16,9 % til 27,0 % i placebogruppen. I alle fase 3-studierne er der ikke en nævneværdig forskel mellem grupperne i forhold til raten af mindst et tilfælde af *suicidal ideation* for patienter, der **ikke** har *suicidal ideation* ved baseline (nul point i C-SSRS). I SUSTAIN-1 observeres højere C-SSRS score hos nogle patienter uden dog at nå skæregrænsen for *suicidal ideation*: Induktionsfasen: 42/362 (11,6 %) patienter med højere score (direkte indtrådte patienter); optimeringsfasen: 22/386 (5,7 %) patienter med højere score (direkte indtrådte + overførte patienter); vedligeholdelsesfasen: 3/125 (2,4 %) vs. 6/133 (4,5 %) patienter med højere score i hhv. esketamin-gruppen og patienter, der randomiseres til placebo (direkte indtrådte + overførte patienter). For patienter på tværs af fase 3-studierne, der **ikke** har *suicidal ideation* ved baseline, men oplever forværring, er der ingen nævneværdig forskel mellem grupperne.

For patienter på tværs af fase 3-studierne, der **har en positiv score** for *suicidal ideation* ved baseline, udviser fem patienter (alle i esketamingruppen) selvmordsrelateret adfærd i esketamingruppen. I alt er 10 patienter i fase 3-studierne registeret med selvmordsrelateret adfærd i esketamingruppen (bestemt ved en score på 6-10 point, C-SSRS) – alle med en livslang historik for samme. I SUSTAIN-2 rapporteres, at *suicidal ideation* optræder hos 5,2 % af patienterne. Alvorlige *suicidal ideation* udgør under 1 % i alle fase 2- og 3-studierne [redacted]

Dissociative symptomer
På tværs af alle fase 2- og fase 3-studier er dissociative symptomer den hyppigst forekommende psykologiske bivirkning ved behandling med esketamin og optræder hos 12,5 - 27,6 % af studiedeltagerne. [redacted]
Symptomerne er generelt af forbigående og milde til moderate af karakter. Dissociative symptomer ses i meget begrænset omfang i placebogruppen (0 - 3,6 %). Herudover observeres højere andel af dissociative symptomer ved behandling med esketamin 84 mg (23,8 %) vs. 56 mg (17,4 %) undersøgt i TRANSFORM 1, hvor der var fixed dosering. I TRANSFORM-1, -2,-3 og SUSTAIN-1,-2 blev 95 % af tilfældene rapporteret på dagen for administrationen, og de forsvandt i de fleste tilfælde igen samme dag. I SUSTAIN -3 sås et lignende mønster, hvor 90 % af tilfældene forsvandt samme dag, og de varede i gennemsnit 0,9 timer.

Det almindelige forløb er en stigning i totalscoren målt med *Clinician Administred Dissociative States* (CADSS, range: 0-92 point, 0-4 = normalt niveau), der peaker efter 40 min. og typisk falder til baselineniveau indenfor 1,5 time. Den maksimale middelværdi på tværs af fase 2- og fase 3-studier overstiger ikke 10 point på CADSS, og i både TRANSFORM-studierne og SUSTAIN-1 og -2 observeres et gradvist fald over gentagen administration af esketamin.

Severe dissociative symptomer beskrives hos færre end 4 % af patienterne på tværs af studierne. I SUSTAIN-2 og -3 udgør dissociative symptomer hhv. 1,9 % og 2,2 % af alle *severe* TEAE'er og er dermed den hyppigst forekommende *severe* TEAE i SUSTAIN-2 og den anden hyppigste i SUSTAIN-3 [25]. En post-hoc analyse udført på TRANSFORM-1 og -2 viser en korrelation mellem incidensen af dissociative symptomer ved uge 1 og uge 2 – 4, dvs. de patienter, der ikke oplevede dissociation ved uge 1, havde under 10 % risiko for at opleve dissociative symptomer ved de efterfølgende esketaminbehandlinger. Omvendt havde de, der oplevede dissociative symptomer i uge 1 mellem 71,4 - 94,0 % risiko for at opleve dissocition ved uge 4.

Psykose-lignende symptomer
Ingen psykose blev observeret på tværs af de afsluttede fase 2- og fase 3-studier, og generelt forsvandt de psykoselignende symptomer, der blev registreret med *Brief Psychiatric rating Scale* (BPRS, range: 0-24 point) indenfor 1,5 time efter administration. Andelen af patienter med en totalscore ≥ 3 point på BPRS var væsentlig større i esketamingruppen sammenlignet med placebo i fase 3-studierne (op til 28,1 % vs. 1,8 % i placebogruppen i TRANSFORM-2). Det er ikke tydeligt, hvilken klinisk betydning dette har (EPAR) [redacted]

Angst
Ifølge EPAR optræder angst TEAE's i højere grad i esketamingruppen, sammenlignet med placebogruppen hos voksne (esketamin overfor placebo; 9,0 % vs. 5,4 % i TRANSFORM-1 og -2, og 7,9 % vs. 3,4 % i vedligeholdelsesfasen af SUSTAIN-1). Det modsatte var tilfældet hos de ældre (esketamin overfor placebo; 4,2 % vs. 7,7 % i TRANFORM-3).

Vurderet ud fra det ukontrollerede sikkerhedsstudie SUSTAIN-2 ses der umiddelbart ikke en ændring i tilfælde af angst over tid. Studiet rapporterer angst hos 9,0 % i esketamin-gruppen. Angstanfaldene var primært milde til moderate i sværhedsgrad og selvbegrænsende. *Severe* TEAE's som følge af angst i esketamin-gruppen blev rapporteret blandt 0,3 - [redacted] % af studiedeltagerne på tværs af studierne. Ifølge EPAR er angst en bivirkning (*adverse drug reaction*) af esketamin. Svær og ekstreme angsttilfælde, der resulterer i panikanfald, eller der leder til ophør af behandling, er fåtallige. Under 4 % af angsttilfældene i esketamingruppen blev behandlet med medicin. [redacted]

Tilfælde af mani
Tre tilfælde af mani er registreret på tværs af de afsluttede fase 2- og fase 3-studier. Det ene blev registreret efter første dosis af esketamin + OAD (duloxetin) og varede 7 dage og blev vurderet til muligvis at være relateret til esketaminbehandlingen. Det andet fandt sted på dag 38 og varede til dag 65 og blev ikke vurderet til at være relateret til esketaminbehandlingen. Det tredje tilfælde blev karakteriseret som eufori og fandt sted i løbet af en follow-up fase ved fire separate hændelser (dag 1, 4, 18 og 25). [redacted] Det er uklart, hvordan patienter med en udiagnosticeret maniodepressiv tilstand vil reagere på esketaminbehandling.

Forhøjet blodtryk
Forhøjet blodtryk beskrives i studierne som en forbigående (primært asymptomatisk) stigning i systolisk og diastolisk blodtryk, der forekommer umiddelbart efter administration af esketamin. Den maksimale gennemsnittelige ændring i blodtryk nås typisk indenfor 40 minutter efter administration og falder til udgangspunktet indenfor 1,5 time.

På tværs af fase 3-studierne er observeret abnorme stigninger i blodtryk, defineret som systolisk blodtryk ≥ 180 mm Hg og/eller diastolisk blodtryk ≥ 110 mm Hg (tilsvarende akut hypertension) hos op til 5 % i esketamingruppen (vs. 0,9 % i placebogruppen i TRANSFORM-1/2) med undtagelse af ældrepopulationen i TRANSFORM-3, hvor 11,1 % i esketamingruppen (vs. 6,2 % i placebogruppen) oplevede forbigående forhøjet blodtryk. På tværs af fase 2 og 3-studierne ses få severe/serious TEAEs relateret til blodtryks-stigninger eller hurtig puls (takykardi), og generelt ledte disse symptomer ikke til behandlingsophør (< 2 %).

Mellem 90 % - 100 % af de forhøjede blodtryk optræder på administrationsdagen. Op mod 7 % af disse normaliseres ikke spontant samme dag. Ifølge en subgruppeanalyse optræder kardiovaskulære hændelser hyppigere blandt patienter med kardiovaskulære risikofaktorer. Ingen klinisk signifikante ændringer i EKG i hverken esketamin- eller placebogruppen er observeret.

Esketamin er kontraindiceret hos patienter, hvor en stigning i blodtrykket eller intrakranielt tryk udgør en alvorlig risiko. Det gælder bl.a. patienter med aneurysmal karsygdom (herunder i intrakranielle kar, kar i thorax eller aorta abdominalis eller

perifere arterier), patienter der tidligere har haft hjerneblødning og patienter med nylig (inden for 6 uger) kardiovaskulær hændelse, herunder myokardieinfarkt.

Afhængighed
Ifølge EPAR har esketamin samme misbrugspotentiale som ketamin. Behandling af behandlingsresistent depression med esketamin, som estimeret af ansøger, svarer til et kronisk brug af et dissociativt medikament. I den tidligere vurdering har fagudvalget derfor fremhævet, at der skal være opmærksomhed omkring, hvilke utilsigtede effekter der potentielt kan forekomme ved kronisk/vedvarende brug inkl. risiko for udvikling af misbrug (af esketamin eller ketamin).

På baggrund heraf påpeger ansøger i deres genansøgning, at der i ingen af de afsluttede fase 3-studier er registreret patienter, som skulle have ønsket én øget dosis eller frekvens af deres esketaminbehandling. Det oplyses desuden, at der i ingen af de gennemførte studier er rapporteret nogle TEAE'er som medicinmisbrug eller overdosering. Dog er der i de afsluttede fase 2- og 3-studier rapporteret langt flere TEAE's *suggestive of drug abuse* i esketamin + OAD-gruppen (51,1 %) ift. placebo + OAD-gruppen (12,8 %) i de dobbeltblindet studier. Dette gav en odds ration (OR) på 7,2 [5,2; 9,9]. På tværs af alle studierne ses, at 54,4 % af patienter behandlet med esketamin oplevede én eller flere TEAE'er *suggestive of drug abuse.* De mest almindelige TEAS' er *suggestive of drug abuse* var svimmelhed, dissociation og somnolence. Disse events blev rapporteret kort efter administration af esketamin og er karakteriseret som kortvarige og hovedsagelig af milde (56,1 %) til moderate (37,8 %) i intensitet. På tværs af alle de afsluttede studier ses fire event (0,2 %), som karakteriseres som *seriouse TEAEs suggestive of abuse potential,* hvoraf ingen blev vurderet til at være relateret til esketaminbehandlingen.

[redacted]

Samlet vurdering af effektmålet uønskede hændelser
Overordnet set ændrer den nye gennemgang ikke på fagudvalgets tidligere konklusioner vedr. sikkerhed.

Fagudvalget finder, at esketamin aggregeret ikke kan kategoriseres vedr. uønskede hændelser. Fagudvalget vurderer, at der ikke er betydende klinisk forskel mellem esketamin og placebo for andel af patienter, der oplever én eller flere SAE, og andel der ophører pga. uønskede hændelser indenfor 4 ugers behandling.

Fagudvalget vurderer, ud fra den narrative gennemgang af data fra studier og EPAR, at der ikke er nævneværdig øget behandlingsophør grundet uønskede hændelser eller øget forekomst af dødsfald efter behandling med esketamin sammenlignet med placebo.

Fagudvalget fremhæver dog, at dissociative symptomer kan variere betydeligt i deres sværhedsgrad og finder fortsat, at graden eller omfanget af de dissociative symptomer er utilstrækkeligt beskrevet for studiepopulationerne. Fagudvalget udtrykker derfor fortsat generelt bekymring for dissociative symptomer og fremhæver, at nogle patienter højest sandsynligt vil opleve de dissociative symptomer som meget ubehageligt, ligesom nogen vil have en risiko for efterfølgende at få generende *flashbacks* relateret til disse.

Herudover mener fagudvalget fortsat ikke, at blodtryksstigninger forbundet med anvendelse af esketamin er tilstrækkeligt belyst. Fagudvalget tilslutter sig, at alle patienter, der behandles med esketamin, bør overvåges efter dosering på grund af muligheden for sedation, dissociation og forhøjet blodtryk. Overvågning skal ske af en sundhedsperson, indtil patienten anses for at være klinisk stabil og parat til at forlade klinikken (inkl. revurdering af patientens blodtryk efter ca. 40 minutter og efterfølgende, som det findes klinisk relevant) [25].

Fagudvalget vurderer, at bivirkningsprofilen ved esketamin er bekymrende og betydende for, hvilke patienter man bør tilbyde behandlingen til og hvor i behandlingsalgoritmen esketamin evt. ville kunne afprøves. Fagudvalget vurderer, at lægemidlets påvirkning af nervesystemet, herunder svimmelhed, dissociation og somnolens, er bekymrende, sidstnævnte også i forhold til bilkørsel. Disse neuropsykiatriske og motoriske forstyrrelser er potentielt alvorlige bivirkninger og bekræftes af, at der kræves overvågning af sundhedsperson efter hver administration.

Generelt er fagudvalget bekymret for, at esketamin kan vise sig at have lignende uønskede effekter, herunder misbrugspotentiale, som det ses fra studier med ketamin [26,27].

5.2.6 Fagudvalgets konklusion for klinisk spørgsmål 1

Fagudvalget vurderer, at den samlede værdi af esketamin i kombination med SSRI eller SNRI sammenlignet med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode, **ikke kan kategoriseres** efter Medicinrådets metoder. Den samlede kategori for lægemidlet og kvaliteten af den samlede evidens fremgår af Tabel 3.

Fagudvalget vurderer, at esketamin i kombination med SSRI eller SNRI kan have en gavnlig kortidseffekt hos nogle patienter. Antallet af patienter, der opnår denne effekt i sammenligning med SSRI eller SNRI alene, er dog relativt beskedent, vurderet ud fra datagrundlaget. Hos en andel med umiddelbar effekt af behandlingen ser det ud til, at effekten er vedvarende i op til 6 måneder. Den længerevarende effekt af esketamin er fortsat ikke tilstrækkeligt belyst i sammenligning med relevant komparator. Samtidig er det data, som ligger til grund for kategoriseringen baseret på selekterede patienter, som ikke afspejler dansk klinisk praksis. Der er herudover fortsat usikkerhed omkring effekten af at stoppe esketamin efter længere tids behandling. Fagudvalget udtrykker samtidig bekymring for bivirkningsprofilen, herunder særligt lægemidlets påvirkning af nervesystemet (svimmelhed, dissociation og somnolence), eventuelle længerevarende

og irreversible bivirkninger, som endnu ikke er tilstrækkeligt belyst samt det misbrugspotentiale, som er forbundet med anvendelse af lægemidlet.

Fagudvalget vurderer, at bivirkningsprofilen ved esketamin er bekymrende og betydende for, hvilke patienter man bør tilbyde behandlingen til og hvor i behandlingsalgoritmen esketamin evt. ville kunne afprøves. Samlet set vurderer fagudvalget, at esketamin ikke vil være et relevant behandlingsvalg for hele gruppen af patienter med behandlingsresistent depression ud fra den anvendte definition.

I spørgsmål 2 vurderer fagudvalget data for en subgruppe af patienter med mere svær grad af sygdom defineret ved MSM $\geq$ 9

5.3 Klinisk spørgsmål 2

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med moderat til svær behandlingsresistent depression vurderet ud fra MSM (MSM $\geq$ 9) i den aktuelle moderate til svære depressive episode?

5.3.1 Litteratur

Til besvarelse af kliniske spørgsmål 2 har ansøger, i forbindelse med genansøgningen, anvendt data fra TRANSFORM-1, -2 og -3 samt data fra SUSTAIN-2 og TRD-kohorten. Studierne, generelle studie- og populationskarakteristika, er gennemgået i afsnit 5.1.1. Subpopulation med MSM ≥ 9 er ikke publiceret og er derfor data on file. Data vurderes, at være relevant og nødvendigt for vurderingen.

Populationskarakteristika
Jævnfør protokollen ønskes effekten af esketamin + OAD vurderet hos patienter over 18 år med moderat til svær behandlingsresistent depression, som har en score på 9 eller derover på MSM. TRD-patienter defineres i denne sammenhæng som patienter, som ikke har responderet på to forskellige typer antidepressiva, givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger), eller har haft depression i to eller flere år (samme episode) uanset behandling. I esketaminstudierne udgør subpopulationen med MSM ≥ 9 mellem [redacted] af de samlede populationer.

Fagudvalget vurderer, at populationen er mere behandlingsrefraktære end den fulde population, men at de samme forbehold vedr. komorbiditet og ECT som eksklusionskriterie er relevante for denne subpopulation. En del af disse patienter ville i dansk praksis på dette tidspunkt i deres depressionsforløb have afprøvet ECT.

5.3.2 Databehandling og analyse

I dette afsnit beskrives ansøgers datagrundlag, databehandling og analyser anvendt til besvarelse af klinisk spørgsmål 2.

Protokollen definerer to relevante måletidspunkter (min. 4 uger og min. 6 måneder) for at belyse hhv. den hurtigindtrædende effekt og den vedvarende effekt af esketamin for

subgruppen TRD-patienter med en MSM-score ≥ 9. Begge måletidspunkter er vurderet lige vigtige og vægtes ens, jf. protokollen.

Den endelige ansøgning inkluderer metanalyser af TRANSFORM-1, -2 og -3, som anvendes til at belyse effektforskellen mellem esketamin + OAD og placebo + OAD for subgruppen ved 4 uger. I disse analyser anvender ansøger en *random-effekt* model. Herudover har ansøger inkluderet en indirekte analyse mellem SUSTAIN-2 og TRD-kohorte, som anvenders til at belyse den vedvarende effekt af esketamin ved 6 måneder for subgruppen.

Hændelsesrater korttidsdata
Til beregning af de absolutte forskelle for sammenligning mellem esketamin og placebo efter 4 uger (TRANSFORM-1, -2, og -3) har ansøger anvendt hændelsesraterne fra studierne (komparatorarmene), som var [redacted] for hhv. remission og respons i MSM $\geq$ 9. I protokollen er hændelsesraterne for hhv. remission og respons estimeret til 14 % og 20 % for den samlede TRD-population. Ingen hændelsesrater for MSM ≥ 9 subpopulationen er prædefineret i protokollen. Fagudvalget anvender derfor hændelsesrater fra studierne på subgruppen til trods for, at patienterne i subgruppen som udgangspunkt må betragtes som mere refraktære og herved sværere at behandle end danske patienter grundet de strikse inklusionskriterier. Som konsekvens heraf vurderes resultaterne med forbehold for dette. Samtidig er der stor forskel i komparatorhændelsesraterne i TRANSFORM studier for MSM ≥ 9 populationen. Primært er hændelsesraten for komparator i TRANSFORM 1 meget høj.

Grundet disse forskelle, samt at der er heterogenitet i metaanalyserne af TRANSFORM 1, 2 og 3, opgøres resultaterne også for de individuelle studier separat.

Bivirkninger og sikkerhed
Data for effektmålene *alvorlige uønskede hændelser* og o*phør af behandling som følge af uønskede hændelser* er ikke opgjort af ansøger for subgruppen MSM ≥ 9. Her henvises til den opgørelse for den fulde population, som kan læses i afsnittet 5.2.5.

Medicinrådet har foretaget følgende ændringer af ansøgers beregninger og resultatfremstilling:
På baggrund af de tidligere beskrevne problemstillinger ved den indirekte analyse mellem SUSTAIN-2 og TRD-kohorten, vil denne analyse ikke indgå i vurderingen, og Medicinrådet vil kun gennemgå resultaterne fra SUSTAIN-2 deskriptivt uden brug af komparator (se afsnit 5.2 Databehandling og analyse på side 21).

Håndtering af missing data
Ansøger har på Medicinrådets opfordring udarbejdet nye beregninger for effektmålene, så manglende data ikke bliver inkluderet via *Last Observation Carrried Forward* (LOCF). Hvor det er muligt, rapporterer Medicinrådet beregninger baseret på "*observed cases*", og på "*missing as failure*", også kaldet "*full nonresponder imputation analysis*".

5.3.3 Evidensens kvalitet

Da vurderingen i spørgsmål 2 hovedsageligt baserer sig på en deskriptiv gennemgang af data for enkelte studier, er der ikke lavet en GRADE vurdering. Dette svarer til, at evidensens kvalitet er meget lav.

5.3.4 Effektestimater og kategorier

Tabel 4 herunder ses de absolutte og relative effektforskelle for remission og respons ved hhv. 4 uger og 6 måneder samt livskvalitet relateret til klinisk spørgsmål 2.

Tabel 4. Gennemgang af data relateret til klinisk spørgsmål 2

Studie	MSM ≥ 9			
	Esketamin + OAD (%)	Placebo + OAD (%)	Absolut forskel (CI)	Risk ratio (CI)
Andel der opnår remission ved uge 4 (MADRS total score of ≤ 12)				
TRANSFORM-1	[redacted]	[redacted]		[redacted]
TRANSFORM-2	[redacted]	[redacted]		[redacted]
TRANSFORM-3	[redacted]	[redacted]		[redacted]
Meta-analyse			[redacted]	[redacted]
Andel der opnår remission ved 6 måneder (MADRS total score of ≤ 10)				
SUSTAIN-2	[redacted]			
Andel der opnår respons ved uge 4 (≥ 50 % reduktion fra baseline på total MADRS score)				
TRANSFORM-1	[redacted]	[redacted]		[redacted]
TRANSFORM-2	[redacted]	[redacted]		[redacted]
TRANSFORM-3	[redacted]	[redacted]		[redacted]
Meta-analyse			[redacted]	[redacted]
Andel der opnår respons ved 6 måneder (≥50% reduktion fra baseline på total MADRS score)				
SUSTAIN-2	[redacted]			
Gennemsnittelig ændring fra baseline på EQ-5D-5L ved 4 uger				
TRANSFORM-1, mean (SD)	[redacted]	[redacted]		
TRANSFORM-2, mean (SD)	[redacted]	[redacted]		
TRANSFORM-3, mean (SD)	[redacted]	[redacted]		
Meta-analyse			[redacted]	

DE = Direct entry, CI = konfidensinterval, SD = Standard deviation *heterogenitet i analysen, [i]Udregnet ved brug af hændelsesraten fra studierne (komparatorarmen).

Remission (kritisk) for subgruppen MSM ≥ 9

Måletidspunkt 4 uger, remission for subgruppen MSM ≥ 9
Metaanalysen for andel som opnår remission (MADRAS total score ≤ 12) for subgruppen MSM ≥ 9 efter 4 ugers behandling viser en beregnet relativ forskel på [redacted] til fordel for esketamin. Baseret på den relative effektforskel kan værdien af esketamin foreløbigt ikke kategoriseres vedr. remission for subgruppen MSM ≥ 9, fordi estimatet er for usikkert.

Ansøger har anvendt en hændelsesrate baseret på remissionsraterne i TRANSFORM-studierne. Fagudvalget vurderer, at remissionsraterne er høje. Når man anvender remissionsraten fra studierne på [redacted] er den absolutte effektforskel [redacted] til fordel for esketamin. Forskellen er ikke signifikant eller klinisk relevant.

Metaanalysen har heterogenitet, hvilket betyder, at der kan være problemer med at slå resultaterne sammen i en metaanalyse, da resultaterne er for forskellige. Remissionsraterne for placebogrupperne er forskellige for TRANSFORM-1 vs. TRANSFORM-2 og -3, hvor der i TRANSFORM-1 ses en højere placeboremissionsrate [redacted] Samtidig er der også forskelle i remissionsraten for esketamin, hvor [redacted] opnår remission i TRANSFORM-1, -2 og -3. Den store variation i resultaterne vurderes især at skyldes de få patienter, som inkluderes i subpopulationen MSM ≥ 9. De tidligere beskrevne forskelle i populationerne og doseringsregimer kan også påvirke resultatet. Data præsenteres derfor også separat for hver af de tre TRANSFORM-studier (tabel 5).

TRANSFORM-2 repræsenterer fleksibel dosering med esketamin, hvilket svarer til indikationen og den forventede anvendelse. I TRANSFORM-2 ses en effekt af esketamin, hvor [redacted] af patienterne bringes til remission med esketamin [redacted] med komparator. Fagudvalget bemærker, at estimatet for MSM ≥ 9 er baseret på meget få patienter. I TRANSFORM 1 og 3 med fast dosering ses ingen forskelle mellem esketamin og komparator, og remissionsraterne er numerisk højere med komparator.

Fagudvalget vurderer, at data fra TRANSFORM-2 ser lovende ud, men er bekymret over, at en lignende tendens ikke kan observeres i de øvrige TRANSFORM-studier for subpopulationen. Derudover svækker det tiltroen til resultatet, at der er få patienter [redacted] inkluderet i subpopulationen MSM ≥ 9 i TRANSFORM-2.

Måletidspunkt 6 måneder, remission for subgruppen MSM ≥ 9
I SUSTAIN-2 er remission og respons målt ved 26 uger ved behandling med esketamin i fleksibel dosering. Remission opgøres som MADRS total score ≤ 10. Data opgøres på forskellige måder i forhold til håndteringen af missing data. Med en fuld nonresponder imputation analyse opnåede [redacted] remission ved 26 uger med esketamin + OAD. Opgjort ved en partiel nonresponder analyse var det [redacted] som opnåede remission ved 26 uger. Der findes ikke en egnet komparatorgruppe, som kan anvendes til sammenligning.

Fagudvalget vurderer, at det er positivt, at [redacted] af denne gruppe med mere svær sygdom kan bringes til remission og beholde denne i op til 6 måneder. Til sammenligning

var det ca. 30 % af den fulde patientpopulation, som var i remission i op til 6 måneder. Fagudvalget vurderer, at det er forventeligt, at subpopulationen med MSM9 vil være sværere at bringe til remission end den fulde population, fordi de har mere svær sygdom som udgangspunkt.

Samlet vurdering af effektmålet remission for subgruppen MSM ≥ 9

Fagudvalget vurderer, at data er for usikkert til at kunne udtale sig om effekten på remission i den ønskede subpopulation. Fagudvalget vurderer, at det er positivt, at ca. 20 % af patienter i denne subpopulation, som har meget få behandlingsmuligheder tilbage, kan opnå remission ved 6 måneder. Der mangler dog sammenligning med en repræsentativ komparatorgruppe, som også tager højde for effekten af komparator inkl. placeboeffekten.

Respons (vigtig) for subgruppen MSM ≥ 9

Måletidspunkt 4 uger, respons for subgruppen MSM ≥ 9
Resultat fra metaanalysen efter 4 ugers behandling i subgruppen MSM ≥ 9 viser en beregnet relativ forskel på [redacted] til fordel for esketamin. Baseret på den relative effektforskel, kan værdien af esketamin foreløbigt ikke kategoriseres vedr. respons for subgruppen MSM ≥ 9, fordi estimatet er for usikkert.

Ansøger har anvendt en hændelsesrate baseret på responsraterne i TRANSFORM-studierne for subgruppen. Fagudvalget vurderer, at responsraterne er høje. Når man anvender responsraten fra studierne på [redacted] er den absolutte effektforskel [redacted] til fordel for esketamin.

Metaanalysen har heterogenitet, hvilket betyder, at der kan være problemer med at slå resultaterne sammen i en metaanalyse, da resultaterne er for forskellige. Data præsenteres derfor også for hver af de tre TRANSFORM-studier.

Responsrateren for placebogrupperne er forskellige, TRANSFORM-1 [redacted] vs. TRANSFORM-2 [redacted] og TRANSFORM-3 [redacted] hvor der i TRANSFORM-1 ses en noget højere placeboresponsrate. Samtidig er der også forskelle i responsraterne for esketamin, hvor hhv. [redacted] opnår respons i TRANSFORM-1, -2 og -3. Den store variation i resultaterne tilskrives hovedsageligt de få patienter, som inkluderes i subpopulationen MSM ≥ 9.

TRANSFORM-2 repræsenterer fleksibel dosering med esketamin, hvilket svarer til indikationen og den forventede anvendelse. I TRANSFORM-2 ses en effekt af esketamin, hvor[redacted] af patienterne bringes til respons med esketamin [redacted] Fagudvalget bemærker, at estimatet for MSM ≥ 9 er baseret på meget få patienter.

Fagudvalget vurderer, at data fra TRANSFORM-2 ser lovende ud men er bekymret over, at en lignende tendens ikke kan observeres i de øvrige TRANSFORM-studier. Derudover svækker de få patienter, inkluderet i subpopulationen MSM ≥ 9, tiltroen til resultaterne.

Måletidspunkt 6 måneder, respons for subgruppen MSM ≥ 9
Data opgøres på forskellige måder i forhold til håndteringen af missing data. Med en fuld nonresponder imputation analyse opnåede [redacted] respons ved 26 uger med esketamin + OAD. Opgjort ved en partiel nonresponder analyse var det [redacted] som opnåede respons ved 26 uger.

Fagudvalget vurderer, at det er positivt, at ca. [redacted] af denne gruppe med mere svær sygdom kan opnå respons og beholde dette i op til 6 måneder. Til sammenligning var det ca. 45 % af den fulde patientpopulation, som var i respons i op til 6 måneder. Fagudvalget vurderer, at det er forventeligt, at subpopulationen med MSM9 vil være sværere at bringe til respons end den fulde population, fordi de har mere svær sygdom som udgangspunkt.

Samlet vurdering af effektmålet respons for subgruppen MSM ≥ 9
Fagudvalget vurderer, at data er for usikkert til at kunne udtale sig om effekten på remission i den ønskede subpopulation. Fagudvalget vurderer, at det er positivt, at ca. [redacted] af patienterne i denne subpopulation, som har meget få behandlingsmuligheder tilbage, kan opnå remission ved 6 måneder. Der mangler dog sammenligning med en repræsentativ komparatorgruppe, som også tager højde for effekten af komparator inkl. placeboeffekten.

Livskvalitet (vigtigt) for subgruppen MSM ≥ 9

Måletidspunkt 4 uger, livskvalitet for subgruppen MSM ≥ 9
Der er leveret data fra de tre TRANSFORM-studier i subgruppen MSM ≥ 9. Hændelsesraten til beregning af den absolutte forskel er hentet fra studierne. Resultat fra metaanalysen efter 4 ugers behandling viser på tværs af de tre studier en absolut forskel på [redacted] Dette svarer til resultatet i den fulde population.

Måletidspunkt 6 måneder, livskvalitet for subgruppen MSM ≥ 9:
Ingen data for dette effektmål for subgruppen MSM ≥ 9 ved 6 måneder.

Samlet vurdering af effektmålet livskvalitet
Fagudvalget vurderer, at esketamin aggregeret **ikke kan kategoriseres** efter Medicinrådets metoder vedr. livskvalitet, idet den længerevarende effekt ikke er tilstrækkeligt belyst i sammenhæng med relevant komparator. Ved 4 uger ses ingen forskel til komparator.

5.3.5 Fagudvalgets konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at den samlede værdi af esketamin i kombination med SSRI eller SNRI *sammenlignet med SSRI eller SNRI til voksne med behandlingsresistent depression vurderet ud fra MSM (MSM ≥ 9) i* den aktuelle moderate til svære depressive episode, **ikke kan kategoriseres** efter Medicinrådets metoder.

Data er sparsomt for subpopulationen af patienter, som har behandlingsresistent depression af mere svær grad, repræsenteret ved en MSM-værdi ≥ 9, idet

subpopulationen kun udgør mellem [redacted] patientpopulationerne. Fagudvalget vurderer, at data er for usikkert og heterogent til at kunne udtale sig sikkert om effekten i denne ønskede subpopulation i sammenligning med komparator.

Fagudvalget vurderer, at det er positivt, at ca. [redacted] af patienterne i denne subpopulation, som har meget få behandlingsmuligheder tilbage, kan opnå remission ved 6 måneder. Der mangler dog sammenligning med en repræsentativ komparatorgruppe, som også tager højde for effekten af komparator inkl. placeboeffekten. Den længerevarende effekt af esketamin er derfor fortsat ikke tilstrækkeligt belyst i sammenligning med relevant komparator.

Fagudvalget vurderer, at data tyder på, at en mindre andel af patienter - også i denne subpopulation - kan have gavnlig effekt af esketamin i kombination SSRI eller SNRI, og at effekten kan vare ved i op til 6 måneder.

Samtidig har esketamin betydende bivirkninger. Fagudvalget udtrykker bekymring for bivirkningsprofilen, herunder særligt lægemidlets påvirkning af nervesystemet (svimmelhed, dissociation og somnolence), eventuelle længerevarende og irreversible bivirkninger, som endnu ikke er tilstrækkeligt belyst samt det misbrugspotentiale, som er forbundet med anvendelse af lægemidlet.

Fagudvalget vurderer, at i en population med svær behandlingsresistent depression repræsenteret ved MSM $\geq$ 9 vil patienterne være mere tilbøjelige til at acceptere en større risiko for bivirkninger, fordi der ikke er mange alternative behandlingsmuligheder tilbage, og fordi patienternes livskvalitet i forvejen er meget nedsat. Fagudvalget vurderer dog samtidig, at grundet bivirkningernes neuropsykiatriske karakter vil der være en del patienter, som ikke vil ønske at tage imod behandlingen.

Ud fra fagudvalgets vurdering ville esketamin kunne være en aktuel mulighed, når følgende behandlinger har været forsøgt (eller er udelukket):

- kognitiv terapi eller anden relevant form for psykoterapi
- andre strategier (augmentering med litium eller antipsykotika)
- ECT
- Isocarboxazid.

Samtidig vil opstart på behandling forudsætte, at patienten er grundigt udredt forinden bl.a. mht. følgende punkter:

- Er diagnosen korrekt?
- Foreligger der uopdaget misbrug af alkohol eller euforisende stoffer?
- Er relevante somatiske sygdomme, der kan udløse eller vedligeholde depressive symptomer, udelukket eller velbehandlet?
- Har man udelukket bivirkninger ved andre medikamenter, som patienten modtager?
- Har compliance været sikret i tilstrækkelig grad ved de hidtidige behandlingsforsøg?

6. Andre overvejelser

Praktiske aspekter ved administration af esketamin
Ansøger oplyser, at en post-hoc analyse viste, at ≥ 90 % af alle patienter, der modtog esketamin, kunne forlade afdelingen efter 90 min. Det oplyses desuden, at der er praktisk erfaring med, at én til to sygeplejersker kan observere/supervisere seks patienter. Ansøger argumenterer desuden for, at den danske psykiatri allerede har den nødvendige infrastruktur, som behøves for supervision og observation af patienter i esketaminbehandling, da patienter, der f.eks. modtager olanzapin, allerede observeres i minimum 3 timer efter hver injektion, ligesom patienter, der har modtaget ECT, skal observeres i 30-60 min i et observationsrum.

Adhærens til behandling
Esketamin skal selvadministreres under supervision af sundhedsfagligt personale, hvilket betyder, at patienter fysisk skal indfinde sig på den klinik eller afdeling, der er godkendt til at foretage behandlingen. Besøgene vil skulle aflægges lige så frekvent, som esketamin skal administreres (fleksibelt i starten to gange ugentligt og senere ugentligt eller hver anden uge) og i lige så lang tid, behandling varer (ifølge den endelige ansøgning i snit 36 uger). Patienterne skal monitoreres i mindst en time pr. besøg. Ansøger har tilkendegivet, at der i de studier, der foreligger, ikke er registreret problemer med adhærens til behandling i de tilfælde, hvor patienterne har haft et behandlingsrespons. Det fremhæves herudover af ansøger, at det kontrollerede behandlingsforløb vil have karakter af monitorering, så der kan gøres de nødvendige tiltag for, at patienterne fortsætter i behandling. Fagudvalget vurderer det sandsynligt, at nogle patienter, der ikke godkendes til behandling med esketamin, vil forsøge at selvmedicinere med ketamin eller opsøge private klinikker i Danmark eller udlandet, hvor der behandles med ketamin.

Grafisk præsentation af individdata
Fagudvalget havde i protokollen efterspurgt ændringer i MADRS-scoren præsenteret grafisk over perioden fra baseline til endt opfølgning som spaghetti-plots for de individuelle patienter med en score på 9 eller derover på MSM for at vurdere, om der er en sammenhæng mellem behandling og ændring i depressive symptomer over kortere tidsintervaller og/eller på individniveau. Ansøger har ikke indleveret disse data.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Poul Videbech *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Gustav Bizik *Overlæge*	Region Nordjylland
Udpegning i gang	Region Midtjylland
Claus Havregaard Sørensen *Overlæge*	Region Syddanmark
Dénes Langyel *Overlæge*	Region Sjælland
Lars Vedel Kessing *Professor, overlæge*	Region Hovedstaden
Niels August Willer Strand *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Jonas Meile *Speciallæge i almen medicin*	Dansk Selskab for Almen Medicin
Klaus Martiny *Professor*	Inviteret af formanden
Martin Balslev Jørgensen *Professor, overlæge*	Inviteret af formanden
Leni Grundtvig Nielsen Patient/patientrepræsentant	Danske Patienter
Louise Wulff Patient/patientrepræsentant	Danske Patienter

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	13.01.2022	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 5. Vurdering af risiko for bias Fedgchin et al., 2019, TRANSFORM-1, NCT02417064 [17]

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Computergenereret randomisering process. Der stratificeres på baggrund af land og kategori af oral antidepressiva. Baslinekarakteristikkerne i armene antyder en balanceret randomisering.
Effekt af tildeling til intervention	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antideprissiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser blev udført på fuldt analyse sæt, defineret som alle randomiserede patienter som modtog ≥ 1 dosis af studiemedicinen og OAD. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede patienter som modtog ≥ 1 dosis af studiemedicinen eller OAD. Der er transparent frafald i alle behandlingsarme. Esketamin 56mg + OAD (n=6), Esketamin 84mg + OAD (n=19), Placebo + OAD (n=6).
Risiko for bias ved indsamlingen af data	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antidepressiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration. Da de dissociative effekter ved esketamin kunne resultere i ublinding af det tilstedeværende personale, blev MADRAS-vurderingen fortaget telefonisk af blindet personale.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Sammenhold af artikel med information på clinicaltrials.gov viser ingen selektiv rapportering.
Overordnet risiko for bias	**Forbehold**	Der er overordnet set forbehold vedr. risiko for bias.

Tabel 6. Vurdering af risiko for bias Popova et al., 2019, TRANSFORM-2, NCT02418585 [18]

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Computergenereret randomisering proces. Der stratificeres på baggrund af land og kategori af oral antidepressiva. Baslinekarakteristikkerne i armene antyder en balanceret randomisering.
Effekt af tildeling til intervention	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antideprissiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser blev udført på fuldt analyse sæt, defineret som alle randomiserede patienter, som modtog ≥ 1 dosis af studiemedicinen og OAD. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, som modtog ≥ 1 dosis af studiemedicinen eller OAD. Sammenligneligt frafald i armene (esketamin + OAD, n=13 og Placebo + OAD, n=9).
Risiko for bias ved indsamlingen af data	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antidepressiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration. Da de dissociative effekter ved esketamin kunne resultere i ublinding af det tilstedeværende personale, blev MADRAS-vurderingen fortaget telefonisk af blindet personale.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Sammenhold af artikel med information på clinicaltrials.gov viser ingen selektiv rapportering
Overordnet risiko for bias	**Forbehold**	Der er overordnet set forbehold vedr. risiko for bias.

Tabel 7. Vurdering af risiko for bias Ochs-Ross et al., 2020, TRANSFORM-3, NCT02422186 [19]

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Computergenereret randomisering process. Der stratificeres på baggrund af land og kategori af oral antidepressiva. Baslinekarakteristikkerne i armene antyder en balanceret randomisering.
Effekt af tildeling til intervention	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antideprissiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration.
Manglende data for effektmål	**Lav**	Alle effektivitetsanalyser blev udført på analyse sæt, der inkluderede alle randomiserede patienter, som modtog ≥ 1 dosis af studiemedicinen og OAD. Sikkerhedsanalyser blev udført på sikkerhedspopulationen, som omfattede alle patienter, der modtog ≥ 1 dosis af studiemedicinen eller OAD. Der er transparent frafald i begge behandlingsarme (esketamin + OAD, n = 10 og Placebo + OAD, n = 6).
Risiko for bias ved indsamlingen af data	**Forbehold**	Studiet er dobbelt-blindet ift. esketamin, men open-label ift. det nye antideprissiva. Det er muligt, at patienter og tilstedeværende personale kan have ræsonneret sig frem til, om patienten modtog esketamin baseret på patientens oplevelse ved administration. Da de dissociative effekter ved esketamin kunne resultere i ublinding af det tilstedeværende personale, blev MADRAS-vurderingen fortaget telefonisk af blindet personale.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Sammenhold af artikel med information på clinicaltrials.gov viser ingen selektiv rapportering
Overordnet risiko for bias	**Forbehold**	Der er overordnet set forbehold vedr. risiko for bias.

Bilag 2: GRADE

Tabel 9. GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Esketemin	Komparator	Relativ (95 % CI)	Absolut (95 % CI)		
Alvorlige uønskede hændelser (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Alvorlig[c]	Ingen	6/418 (1,4 %)	3/287 (1,0 %)	RR: 1,40 [0,37; 5,29]	0,4 %-point [-0,63; 4,39]	⨁◯◯◯ MEGET LAV	KRITISK
Behandlingsophør grundet uønskede hændelser (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Alvorlig[c]	Ingen	20/418(4,8 %)	5/287 (1,7 %)	RR: 2,60 [0,97; 6,99]	2,72 %-point [0,05; 10,18]	⨁◯◯◯ MEGET LAV	KRITISK
Remission, MADRAS score ≤ 12 (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ingen	142/373(38 %)	68/268(25 %)	RR: 1,50 [1,10; 2,04]	7,0 %-point [1,4; 14,6]	⨁⨁◯◯ LAV	KRITISK
Respons, andel der reducerer MADRS score med 50 % eller mere (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ingen	199/373(53 %)	102/268(38 %)	RR: 1,38 [1,16; 1,63]	7,6 %-point [3,2; 12,6]	⨁⨁◯◯ LAV	VIGTIGT
Livskvalitet, gennemsnitlig ændring fra baseline på EQ-5D index score (4 uger)												
3	Randomiserede forsøg	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ingen	209	286		0,06 point [0,01; 0,10]	⨁⨁◯◯ LAV	VIGTIGT

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio

a. Der er nedgraderet for RoB, idet der er fare for afblinding i studiet grundet esketamins dissociative effekter.

b. Der er betydelig indirekthed i forhold til den danske population pga. studiernes in-/eksklusion kriterier

c. Der nedgraderes for evidensens kvalitet ét niveau pga. unøjagtighed, da usikkerheden om det relative effektestimat kan føre til forskellige konklusioner.

Application for the assessment of clinically added value of Spravato® (esketamine) for treatment resistant depression in adults

Contents

1 Basic information

Table 1 Contact information

Name	Nikolaj Bødker
Title	Health economics, market access and reimbursement manager
Area of responsibility	Market Access
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Title	Field Medical Advisor
Area of responsibility	Medical
Phone	+45 29998264
E-mail	jrisse@its.jnj.com

Table 2 Overview of the pharmaceutical (1)

Proprietary name	SPRAVATO®
Generic name	Esketamine
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	N06AX27
Pharmacotherapeutic group	Psychoanaleptic, Other antidepressants
Active substance(s)	Esketamine hydrochloride
Pharmaceutical form(s)	28 mg Nasal Spray, solution
Mechanism of action	Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.
Dosage regimen	The dose recommendations for Spravato® are shown in Table A and Table B (adults ≥65 years). It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the

<table>
<tr><td></td><td>maintenance phase, Spravato® dosing should be individualised to the lowest frequency to maintain remission/response.

<table>
<tr><th colspan="2">Table A: Recommended dosing for SPRAVATO® in adults <65 years</th></tr>
<tr><th>Induction phase*</th><th>Maintenance phase**</th></tr>
<tr><td><u>Week 1-4:</u>
Starting day 1 dose: 56 mg
Subsequent doses: 56 mg or 84 mg twice a week</td><td><u>Week 5-8:</u>
56 mg or 84 mg once weekly

<u>From week 9:</u>
56 mg or 84 mg every 2 weeks or once weekly</td></tr>
</table>

<table>
<tr><th colspan="2">Table B: Recommended dosing for SPRAVATO® in adults ≥65 years</th></tr>
<tr><th>Induction phase*</th><th>Maintenance phase**</th></tr>
<tr><td><u>Week 1-4:</u>
Starting day 1 dose: 28 mg
Subsequent doses: 28 mg, 56 mg or 84 mg twice a week, all dose changes should be in 28 mg increments</td><td><u>Week 5-8:</u>
28 mg, 56 mg or 84 mg once weekly, all dose changes should be in 28 mg increments

<u>From week 9:</u>
28 mg, 56 mg or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments</td></tr>
</table>

* Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment
** The need for continued treatment should be reexamined periodically</td></tr>
<tr><td>Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)</td><td>SPRAVATO®, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode</td></tr>
<tr><td>Other approved therapeutic indications</td><td>No</td></tr>
<tr><td>Will dispensing be restricted to hospitals?</td><td>Yes . dispensing code A§4-BEGR</td></tr>
<tr><td>Combination therapy and/or co-medication</td><td>SPRAVATO®, in combination with a SSRI or SNRI</td></tr>
<tr><td>Packaging – types, sizes/number of units, and concentrations</td><td><u>SPRAVATO® (esketamine) 28 mg Dose Kit*</u>
1x28 mg Nasal Spray Device, 1 Device, 28 mg esketamine

<u>SPRAVATO® (esketamine) 56 mg Dose Kit*</u>
2x28 mg Nasal Spray Devices, 2 Devices, 56 mg esketamine

<u>SPRAVATO® (esketamine) 84 mg Dose Kit*</u>
3x28 mg Nasal Spray Devices, 3 Devices, 84 mg esketamine

*Each Nasal Spray device contains: esketamine hydrochloride corresponding to 28 mg esketamine; Each device delivers: 2 sprays, 1 spray into each nostril;
Total volume to be delivered (per device): 0.2 mL, equivalent to 28 mg of esketamine</td></tr>
<tr><td>Orphan drug designation</td><td>No</td></tr>
</table>

2 Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor
ANCOVA	analysis of covariance
BEGR	Må kun udleveres til sygehuse. Udlevering sker efter bestemmelserne i lægemidler i udleveringsgruppe A
BP	Blood Pressure
CGI-S	Clinical Global Impression Severity
CI	Confidence Interval
C-SSRS	Columbia Suicide Severity Rating Scale
DBS	Deep Brain Stimulation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life (EuroQol) Group, 5-Dimension, 5-Level (questionnaire)
ESK-NS	Esketamine Nasal Spray
FDA	Food and Drug Administration
F/U	Follow-up
HCP	Health Care Professional
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSI	Health Status Index
IA	Interim Analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IDS-C30	Inventory of Depressive Symptomatology - Clinician-rated, 30-item
IDS-C_{ANX}	Inventory of Depressive Symptomatology – Clinician rating anxiety subscale
IWRS	Interactive Web Response System
LL	Lower Limit
LOCF	Last Observation Carried Forward
LS	Least Squares
LSD	Lsergic acid diethylamide
MA	Maintenance
MADRS	Montgomery-Åsberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MDMA	3,4-methylenedioxy-metamphetamine

MDD	Major Depressive Disorder
MGH-ATRQ	Massachusetts General Hospital- Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
MKRF	Mindste klinisk relevante forskel
MMRM	Mized-Effects Model Using Repeated Measures
MMSE	Mini Mental State Examination
NE	Not Estimable
NMDA	N-Methyl-D-Aspartate
NNT	Number Needed to Treat
OAD	Oral Antidepressant
PBO-NS	Placebo Nasal Spray
PCP	Phencyclidine
PHQ-9	Patient Health Questionnaire, 9-item
PWC-20	Physician Withdrawal Checklist, 20-item
RR	Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SMD	Standardized mean difference
SNRI	Serotonin-Norephinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment Emergent Adverse Event
TRD	Treatment Resistant Depression
UL	Upper Limit
VNS	Vagus Nerve Stimulation
Wk	Week
XR	Extended-Release
Y	Year

3 Summary

Esketamine (Spravato®) in combination with a SSRI or SNRI is an innovative treatment approved by the European Commission on December 19th 2019 for the treatment of adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Spravato® is the first antidepressant specifically indicated for treatment resistant depression (TRD). Whereas almost all of the commonly used OADs act on the monoaminergic pathway, Spravato® has a unique mechanism of action, exerting its effect via transient N-methyl-D-aspartate (NMDA) receptor antagonism which is believed to alter the underlying pathophysiological process of depression. Spravato® is administered nasally providing a non-invasive, patient-acceptable, rapidly absorbed and readily bioavailable route of delivery.

This application presents the basis for the evaluation of the clinically added value of Spravato® in combination with SSRI or SNRI compared to placebo in combination with SSRI or SNRI for the treatment of adults with TRD, which have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode, and for the treatment of adults with treatment resistant depression, which have a MSM ≥ 7, MSM ≥ 8 or MSM ≥ 9 score.

Based on the clinical trials included in this submission the data shows that flexible dosed Spravato® nasal spray, in combination with a SSRI or SNRI, provided statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus placebo in combination with SSRI or SNRI. Furthermore, the extensive evidence on safety, including data from the SUSTAIN-2, SUSTAIN-3, SYNAPSE and ATU cohort report, provided in this application underlines that Spravato in combination with a SSRI or SNRI is a safe treatment.

The meta-analyses based on data from the three short-term induction studies i.e., TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 as well as long term data from the long-term maintenance study SUSTAIN-1 and the indirect treatment comparison of SUSTAIN-2 and the TRD cohort study, showed that treatment with Spravato® results in:

- Significantly higher remission rates at induction, maintenance, and month 6 based on MADRS total score.
- Significantly higher response rates at induction, maintenance, and month 6 based on MADRS total score.
- Significantly increase in quality of life at induction and maintenance as measured by EQ-5D-5L mean difference change in health status index.
- No significant difference in serious adverse events
- No significant difference in discontinuation due to adverse events

Consequently, the recommendation of Spravato® in combination with a SSRI or SNRI, will provide danish TRD patients, who have failed at least two OADs or has a MSM ≥ 9 score, with the possibility to get a new innovative treatment with a novel mode af action, which provides clinically meaningful, rapid, and sustained improvement of depressive symptoms and provides the first new opportunity in treatment for TRD in over 30 years.

4 Introduction

The burden attributed by mental disorders and especially depression pose a massive challenge to Danish society and is a major public health concern. Depression is one of the most common psychiatric disorders and is the leading cause of disability worldwide. The global burden has increased steadily with 18% between 2005-2015 affecting more than 320 million people worldwide. (2) In addition to the depression being a debilitating disease for those affected, mental disorders were the overall contributor to loss of productivity including sick leave, reduced ability to work and disability pension. Importantly, the total costs related to treatment, care and loss of productivity was 4.3 billion DKK annually from depression alone. (3) Major depressive disorder (MDD) is a common debilitating disease characterized by the persistence of negative thoughts and emotions that disrupt mood, cognition, motivation and behavior. It is a highly recurrent psychiatric illness characterized by an increased risk of relapse with increasing frequency and severity of episodes over time. (4)

Treatment resistant depression (TRD) is defined as MDD that has not responded to treatment with at least two oral antidepressants in the current depressive episode. (5, 6) TRD is a severely debilitating and potentially life-threatening disease. Symptoms include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy usual activities, and feelings of worthlessness. These symptoms result in an impaired capacity and inability to work, to the point of complete inability to function, which substantially interferes with social connection, integration and relationships. (7) Symptoms of TRD may last for months or years. In many cases, patients with TRD feel weary of life or have suicidal ideation to the point of suicidal actions approximately 30% of patients with TRD attempt suicide at least once in their lifetime. (8) Furthermore, TRD may develop at any age, but disproportionally affects people of working age which places a substantial burden on care givers and loved ones, the healthcare system, and broader society (9-12)
TRD patients typically suffer from an inadequate treatment response and cycle through numerous OADs primarily SSRIs and SNRIs as there is no single preferred agent for TRD in Danish clinical practice.(9, 13) Despite the available pharmacological treatments, there is a serious unmet need for new and TRD specific treatments with a different mode of action since patients continue failing to achieve the overall treatment goal of remission and recovery with current treatment options. (14, 15)

Designated as a Breakthrough Therapy by the US Food and Drug Administration and as stated above approved by the European Commission on December 19th 2019, Spravato® nasal spray is the first antidepressant specifically indicated for TRD. Data from TRANSFORM-2 and SUSTAIN-1 show that flexible dosed Spravato® nasal spray, in combination with a SSRI or SNRI, provided statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus a newly initiated oral AD plus placebo nasal spray. The new mode of action combined with the unique route of administration results in a rapid response (as early as 24 hours) with clinical meaningful symptom improvement compared with currently available oral ADs. Co-administered with an oral AD, esketamine nasal spray has a rapid onset of action, 20% higher response and remission rates in the short-term, and 50% -70% lower relapse rates among stable remitters and responders, in the long-term versus a newly initiated oral AD plus placebo nasal spray.(16, 17) Consequently, the recommendation of Spravato® in combination with a SSRI or SNRI, will provide TRD patients in Denmark with the possibility to getting an innovative effective treatment.

5 Literature search

A systematic literature search was not conducted as specified in the Medicines Council protocol for evaluation of Spravato® for the treatment of treatment resistant depression in adults. The Medicine Council found that the following studies are consider relevant and can be used to conduct direct comparisons.

- TRANSFORM-1 (NCT02417064)
- TRANSFORM-2 (NCT02418585)
- TRANSFORM-3 (NCT02422186)
- SUSTAIN-1 (NCT02493868)
- SUSTAIN-2 (NCT02497287)
- SUSTAIN-3 (NCT02782104)
- SYNAPSE (NCT01998958)
- Unpublished observational data from report for French National Agency for Medicines and Health Product Safety (ANSM) – i.e., ATU report
- Unpublished observational data from the prospective cohort study, European Standard Clinical Practice – i.e., TRD cohort study

5.1 Relevant studies

Table 3 Relevant studies included in the assessment (16-30)

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Efficacy and Safety of fixed-dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1), Fedgchin et al., Int J Neuropsychopharmacol, 2019	TRANSFORM-1	NCT02417064	**Study Start Date:** August 10, 2015 **Study Completion Date:** February 20, 2018	1 & 2
Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study, Popova et al., Am J Psychiatry, 2019	TRANSFORM-2	NCT02418585	**Study Start Date:** August 7, 2015 **Study Completion Date:** November 6, 2017	1 & 2
Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients with Treatment-Resistant	TRANSFORM-3	NCT02422186	**Study Start Date:** August 20, 2015 **Study Completion Date:** August 10, 2017	1 & 2

Depression – TRANSFORM-3, Am J of Geriatric Psychiatry, 2019				
Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression, Daly et al., JAMA Psychiatry, 2019	SUSTAIN-1	NCT02493868	**Study Start Date:** Oct 1, 2015 **Study Completion Date:** February 15, 2018	1 & 2
Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). The Journal of clinical psychiatry. 2020;81(3).	SUSTAIN-2	NCT02497287	**Study Start Date:** Sep 30, 2015 **Study Completion Date:** Oct 28, 2017	1 & 2
Janssen Research & Development L. Abbreviated Interim #2 Clinical Study Report - An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment resistant Depression - Safety and Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-3). 2020.	SUSTAIN-3	NCT02782104	**Study Start Date:** June 9, 2016 **Estimated Study Completion Date:** Dec 31, 2022	1 & 2
Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA psychiatry. 2018;75(2):139-48.	SYNAPSE	NCT01998958	**Study Start Date:** Jan 27, 2014 **Study Completion Date:** Sep 25, 2015	1 & 2
Janssen-Cilag. Cohort Authorization for Temporary Use, ESKETAMINE JANSSEN 28 mg, nasal spray Final Report: Complete report on cumulative period from 23/09/2019 to 25/03/2020. 2020.	ATU	n/a		1 & 2
Heerlein K, Young AH, Otte C, Frodl T, Degraeve G, Hagedoorn W, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: Baseline patient characteristics. Journal of affective disorders. 2021;283:115-22	TRD cohort study	NCT03373253	**Study Start Date:** Feb 13, 2018 **Study Completion Date:** Jan 24, 2020	1 & 2

5.2 Main characteristics of included studies

5.2.1 TRANSFORM-1

TRANSFORM-1 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged 18–64 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤5 OADs in the current episode of depression). The study consisted of a 4-7-week screening/prospective observational phase, a 4-week double-blind induction phase during which nasal spray treatment sessions occurred twice weekly, and a 24-week post-treatment follow-up phase. (19) Schematic illustrating the study design of TRANSFORM-1 is presented in figure 1 at the end of this section. Furthermore, a detailed overview of the main study characteristics of TRANSFORM-1 is available at table A2.
TRANSFORM-1 was conducted to evaluate the efficacy, safety and tolerability of fixed dose esketamine nasal spray plus a newly initiated OAD (ESK-NS-56mg or -84mg + OAD) versus a newly initiated OAD plus placebo nasal spray (OAD + PBO-NS) for the treatment of TRD in adults aged 18–64 years. The primary efficacy endpoint was change from baseline to day 28 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score defined as change in the 10-item clinician-administered MADRS total score (assessed by an independent, remote rater) from baseline (Day 1 prior to randomisation) to the end of the 4-week double-blind induction phase. (19) The secondary endpoints are available at table A2.

At entry of the study, patients had moderate-to-severe depression (Inventory of Depressive Symptomatology [IDS-C30] total score ≥34 and MADRS total score ≥28). In addition to non-response to ≥1 OAD (≤25% improvement) in the current depressive episode based on historical report, non-response to a different OAD taken at an adequate dose for a total duration of at least 6 weeks was observed prospectively in the screening/prospective observational phase. Subsequently non-responders (defined as ≤25% improvement in the MADRS total score from week 1 to week 4 and a MADRS total score ≥28 at weeks 2 and 4) who were eligible to enter the 4-week double-blind treatment phase discontinued all current antidepressant treatment(s). Consequently, at the time of randomization, patients met the study definition of TRD, which was non-response to ≥2 OADs in the current episode of depression. Key exclusion criteria were suicidal ideation with intent to act within the prior 6 months or suicidal behavior within the prior year; diagnosis of psychotic disorder, bipolar or related disorders; recent history (within prior 6 months) of moderate or severe substance use disorder; and, positive test result(s) for specified drugs of abuse. (19) Further details of the exclusion and inclusion criteria is available in table A2.

A total of 710 patients were screened and 346 enrolled patients were randomised 1:1:1, to receive following treatment regimens beginning from the 4-week induction phase (19):

- ESK-NS (56 mg [fixed dose[1]]) plus a newly initiated OAD twice weekly for 4 weeks (n=117)
- ESK-NS (84 mg [fixed dose]) plus a newly initiated OAD twice weekly for 4 weeks[2] (n=116)
- A newly initiated OAD plus PBO-NS twice weekly for 4 weeks (OAD + PBO-NS; n=113).

In general, the treatment groups were similar with respect to baseline characteristics and the full demographic. The baseline characteristics of patients enrolled in the full analysis set of TRANSFORM-1 are presented in table A2a. The mean (SD) age of all patients was 46.3 (11.19) years, ranging from 18–64 years. Most patients were female (70.5%) and white (76.6%). The majority (57.3%) initiated OAD treatment with an SNRI; 39.8% initiated OAD with duloxetine. Of enrolled patients, 45.3% were in North America, 24.9% in

[1] Not in line with licensed dosing for ESK-NS which is for flexible dosing of ESK-NS.
[2] Patients randomised to receive the 84 mg esketamine dose were started at Day 1 on 56 mg before increasing to 84 mg at Day 4.

Europe, and 29.8% from other regions. The mean (SD) baseline MADRS total score was 37.6 (5.52 [range: 18, 53]), corresponding to severe depression. (1) All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these antidepressant treatments. (19)

Most of the randomized patients (315/346) completed the double-blind phase, however a total of 6 (5.1%), 19 (16.4%), and 6 (5.3%) patients in the ESK-NS 56 mg + OAD, 84 mg + OAD, and OAD + PBO-NS groups, respectively, withdrew prior to completing the treatment phase. Worth mentioning, 11 of the 19 withdrawn patients in the ESK-NS 84 mg + OAD group were withdrawn after only receiving the first dose, which was 56 mg based on the fixed titration in the study design. The higher withdrawal rate in the ESK-NS 84 mg + OAD group did not appear to be due to any new or dose-related safety finding. (19)

As described above the ESK-NS dosing was fixed (56 mg or 84 mg) in TRANSFORM-1 and not in line with licensed dosing for ESK-NS which is for flexible dosing of ESK-NS. Patients randomly assigned to 84 mg ESK-NS received an 84 mg dose on Day 4 and for all subsequent nasal spray treatment sessions. No further adjustment to the ESK-NS dose was permitted for the duration of the double-blind induction phase. (19) Table 4 presents the titration schedule of nasal spray study medication (esketamine or placebo) which was dosed at each nasal spray treatment session in the double-blind induction phase of the TRANSFORM-1 trial.

Table 4: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-1 study (31).

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-1		
Day 1	56 mg	
Day 4	56 mg or 84 mg (as per randomisation)	No further adjustments to the esketamine dose were permitted for the duration of the double-blind induction phase

Dosing of the newly initiated OAD began on Day 1 of the induction phase of the TRANSFORM-1/2/3 trials. All patients were initiated, open-label, on one of four OADs from two classes: an SSRI (escitalopram or sertraline), or an SNRI (duloxetine or venlafaxine XR). Dosing of the OAD was according to local prescribing guidelines with protocol-specified titration to the maximally tolerated dose, as per the titration schedule presented in table 5. Use of the titration schedule was mandatory but if higher doses were not tolerated, a down-titration was permitted based on clinical judgment. However, the patient's dose was not to be lower than the following minimum therapeutic doses at the end of the induction phase (19, 31):

TRANSFORM-1/2:

- Duloxetine: 60 mg/day
- Escitalopram: 10 mg/day
- Sertraline: 50 mg/day
- Venlafaxine XR: 150 mg/day

Table 5: OAD dose titration schedule during the double-blind induction phase – TRANSFROM-1/2 (31).

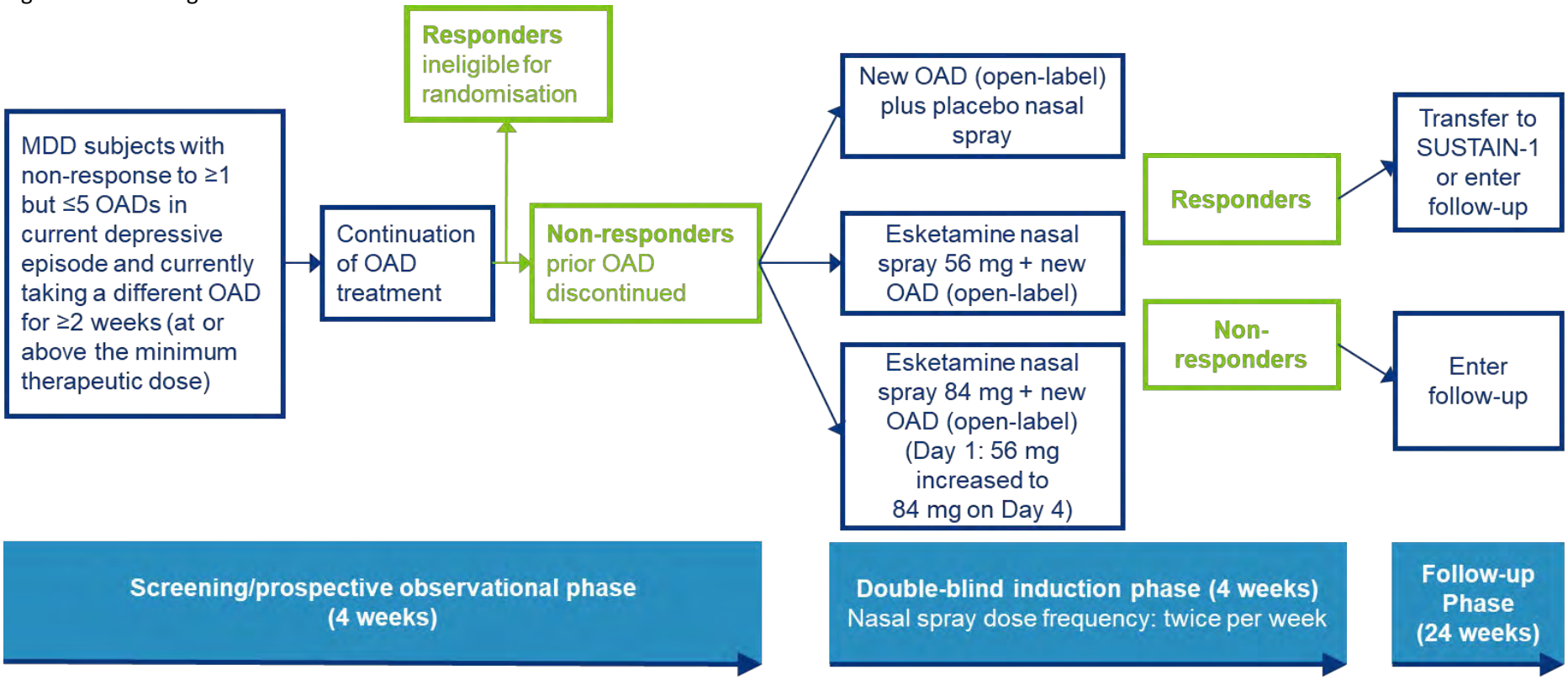
OAD	Titration schedule[a]			
	Week 1 (starting Day 1)	Week 2 (starting Day 8)	Week 3 (starting Day 15)	Week 4 (starting Day 22)
TRANSFORM-1/2				
Duloxetine	60 mg[b]	60 mg	60 mg	60 mg
Escitalopram	10 mg	20 mg	20 mg	20 mg
Sertraline	50 mg	100 mg	150 mg	200 mg (TRANSFORM-1) 150 mg (TRANSFORM-2)
Venlafaxine XR	75 mg	150 mg	225 mg	225 mg

Abbreviations: OAD, oral antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

[a] Adjustments to the titration schedule may have been required in some countries in order to conform to local prescribing information.

[b] In TRANSFORM-1, patients who had a history of increased sensitivity towards SSRIs/SNRIs could, at the discretion of the treating physician, be initiated on a 30 mg dose of duloxetine and up-titrated to the therapeutic dose of 60 mg by the start of Week 2.

Figure 1: Trial design for TRANSFORM-1



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.

5.2.2 TRANSFORM-2

TRANSFORM-2 was a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with recurrent or single-episode TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. TRANSFORM-2 consisted of a 4-7-week screening/prospective observational phase, , a 4-week double-blind induction phase during which nasal spray treatment sessions occurred twice weekly, and a 24-week post-treatment follow-up phase. (16) Schematic illustrating the study design of TRANSFORM-2 is presented in figure 2 at the end of this section. Furthermore, a detailed overview of the main study characteristics of TRANSFORM-2 is available at table A2.1.
The primary objective of TRANSFORM-2 was to evaluate the efficacy of ESK-NS (flexibly-dosed) + a newly initiated OAD versus newly initiated OAD + PBO-NS. The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1 prior to randomization) in clinician-administered MADRS total score (assessed by an independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) to prove efficacy in the context of acute phase treatment. (16) The secondary endpoints are available at table A2.1.

At study entry, participants had documented (retrospectively) nonresponse ≤25% improvement) to ≥1 to ≤5 antidepressants (based on the Massachusetts General HospitalAntidepressant Treatment Response Questionnaire [MGH-ATRQ]) in the current depressive episode and were currently receiving a different OAD, to which they had been adherent (<4 missed days of treatment based on the Patient Adherence Questionnaire) for at least the previous 2 weeks at or above the minimum therapeutic dosage (or therapeutic blood level for specific tricyclic OAD), which was continued prospectively for another 4 weeks during the screening/prospective observational phase, providing a total duration of at least 6 weeks of the prospective OAD. Patients who had not responded to the prospective OAD treatment by the end of the screening phase (nonresponse was defined as ≤25% improvement in MADRS score from week 1 to week 4 and a MADRS score ≥28 at weeks 2 and 4) entered the 4-week double-blind treatment phase, at which time they discontinued all current OAD treatments and were randomly assigned to the intranasal treatment combined with a newly initiated OAD. (16) Key exclusion criteria were current or recent (past 6 months) homicidal ideation/intent or suicidal ideation with intent to act or suicidal behavior within the past year; diagnosis of psychotic disorder, major depressive disorder with psychotic features, bipolar or related disorders, borderline, antisocial, histrionic, or narcissistic personality disorder, obsessive-compulsive disorder (current), intellectual disability, autism spectrum disorder; uncontrolled hypertension; seizures; a recent history (past 6 months) of moderate or severe substance use disorder (including a lifetime history of ketamine use disorder) and positive urine test results for specified drugs of abuse. (16) Further details of the exclusion and inclusion criteria is available in table A2.1.

A total of 435 patients were screened for TRANSFORM-2 of which 227 patients met the inclusion criteria and were randomised to treatment during the double-blind induction phase with either (1, 21):

- ESK-NS (flexibly-dosed: 56 or 84 mg) + a newly initiated OAD (n=116), or
- A newly initiated OAD + PBO-NS (n=111).

However, the full analysis set for ESK-NS (flexibly-dosed: 56 or 84 mg) + OAD was n=114 and for the OAD + PBO-NS n=109. (16) Of the 227 patients randomly assigned to treatment, 197 (86.8%) patients completed the 28 day double-blind induction phase, and 30 (13.2%) patients withdrew. In total, 118 patients continued into SUSTAIN-1.(16)

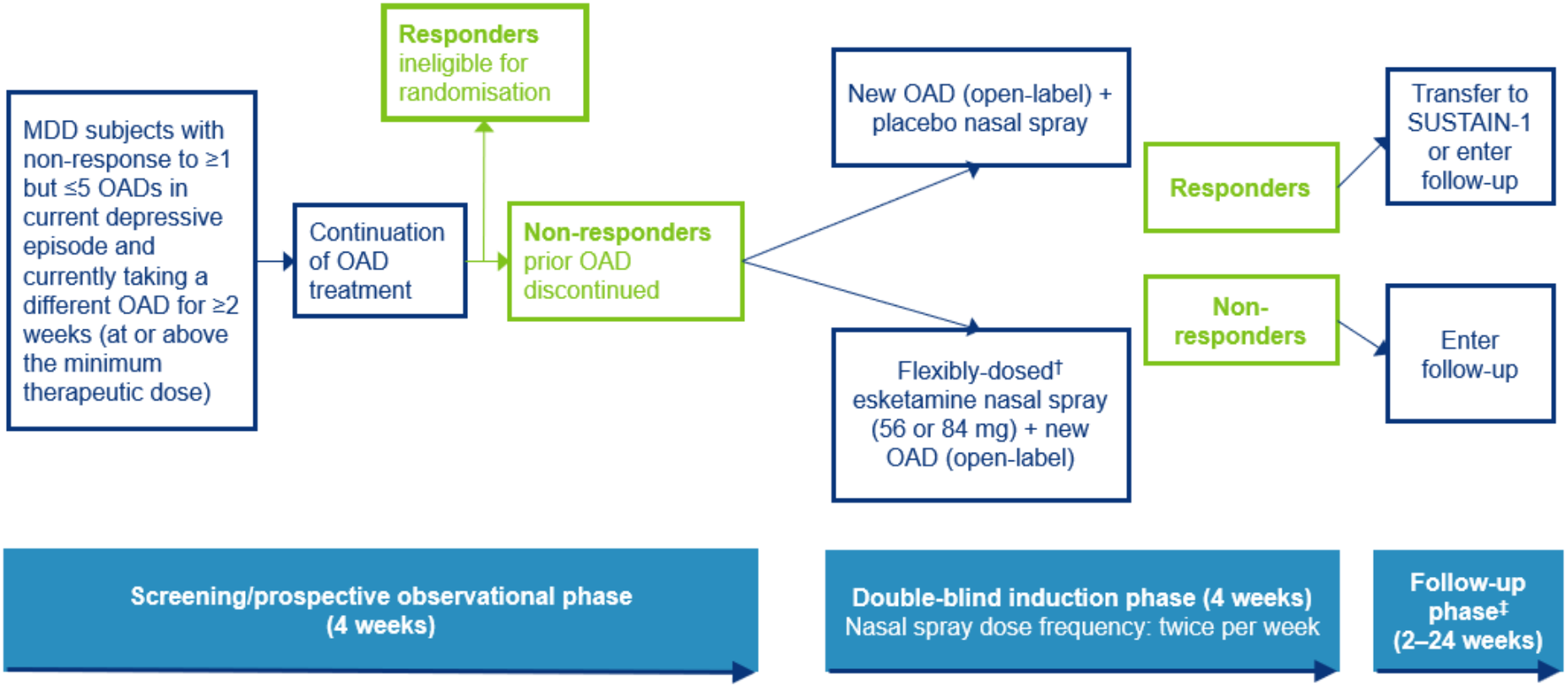
In general, treatment groups were similar with respect to baseline characteristics. The baseline characteristics of patients enrolled in the full analysis set of TRANSFORM-2 are presented in table A2.1a. Patients enrolled in TRANSFORM-2 had a mean baseline MADRS score of 37.1, corresponding to severe depression, a mean age of 45.7 years, and a mean duration of the current episode of MDD of 114.6 weeks. All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these OADs. (1, 16)

As described above TRANSFORM-2 evaluated the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (ESK-NS-56 mg or -84 mg + OAD) versus newly initiated OAD + PBO-NS).
During the double-blind induction phase of TRANSFORM-2, patients self-administered nasal spray treatment (esketamine or placebo) at treatment sessions twice per week for four weeks at the study site. The first nasal spray treatment session occurred on Day 1. On Day 1, patients randomised to receive ESK-NS started on a dose of 56 mg in TRANSFORM-2. (16) At subsequent nasal spray treatment sessions in TRANSFORM-2, the dose could have been titrated as described in table 6.
Dosing of the newly initiated OAD began on Day 1 of the induction phase of the TRANSFORM-2 trial and the subsequently OAD dose titration schedule during the double-blind induction phase is consistent with the titration schedule described in section 5.2.1. (16)

Table 6: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-2 study (32).

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-2		
Day 1	56 mg	
Day 4	56 mg or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8 and 11	56 mg or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84 mg) as determined by the investigator based on efficacy and tolerability.
Day 15	56 mg or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability; no dose increase was permitted on Day 15.
Days 18, 22, and 25	56 mg or 84 mg	The dose was to remain unchanged. If there was no nasal spray treatment session on Day 15, a dose reduction from 84 mg to 56 mg was permitted on Day 18 if required for tolerability; no dose increase was permitted.

Figure 2: Trial design for TRANSFORM-2



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
† On Day 1 of the induction phase, all patients randomised to receive ESK-NS started with a dose of 56 mg. Thereafter, ESK-NS could be dosed flexibly (56 or 84 mg) based on efficacy and tolerability up until Day 15 (or Day 18 if the Day 15 treatment session did not occur). Beyond Day 15, the ESK-NS dose was to remain unchanged. Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.
‡ From the follow-up phase, patients could also transfer to SUSTAIN-3 (ongoing). Non-responders remained double-blinded on their nasal spray treatment.

5.2.3 TRANSFORM-3

TRANSFORM-3 was a 4-week, randomised, double-blind, active-controlled, multicentre, Phase 3 trial that enrolled adult patients (aged ≥65 years) with recurrent or single-episode TRD (non-response to ≥1 but ≤8 OADs in the current episode of depression). Patients aged ≥65 years are generally excluded from Phase 3 antidepressant clinical trials. The ESK-NS clinical trial programme, however, included this dedicated short-term study in patients aged ≥65 with TRD to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS in this vulnerable population. (18)

TRANSFORM-3 consisted of a 4-7-week screening/prospective observational phase assessing response to current OAD treatment, a 4-week double-blind induction phase with flexibly dosed nasal spray study medication (esketamine or placebo) plus a newly-initiated OAD, and a 2-week post-treatment follow-up phase assessing safety and tolerability, including potential withdrawal symptoms. Furthermore, following the 4-week double-blind induction phase, regardless of treatment response, patients could participate in a long-term open-label safety study. Schematic illustrating the study design of TRANSFORM-2 is presented in figure 3 at the end of this section. The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (as assessed by an independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) (18, 22)
Furthermore, a detailed overview of the main study characteristics of TRANSFORM-3 is available at table A2.2.

A total of 302 patients were screened for TRANSFORM-3 of which 138 patients met the inclusion criteria and were randomised 1:1 to treatment during the double-blind induction phase with either (18):

- ESK-NS (flexibly-dosed: 28 mg, 56 mg, or 84 mg) plus a newly initiated OAD twice weekly for 4 weeks (n=72), or
- A newly initiated OAD + PBO-NS twice weekly for 4 weeks (n=66).

In general, the treatment groups were similar with respect to baseline characteristics, see table A2.2a. The mean (SD) age of all patients was 70.0 (4.52) years. Most patients were female (62.0%) and white (94.9%). The majority (55.5%) initiated OAD treatment with an SSRI. Of enrolled patients, 51.1% were in North America, 43.1% in Europe, and 5.8% from other regions. The mean (SD) baseline MADRS total score was 35.2 (6.16 [range: 19, 51]), corresponding to severe depression. Based on Clinical Global Impression-Severity (CGI-S) scores, patients ranged between “mildly ill” and “among the most extremely ill patients”, with approximately half of patients (49.6%) being “markedly ill” and approximately one quarter of patients (24.8%) being “severely ill”. The mean (SD) duration of the current episode of depression was 215.8 (341.71) weeks. Approximately one third (31.9%) of patients had a history (lifetime) of suicidal ideation, assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), and 14.1% had a history (lifetime) of suicidal behaviour. (1)
All patients had non-response to at least two OADs prior to randomisation, with non-response being confirmed prospectively during the screening/prospective observational phase for at least one of these OAD treatments. (18)

Of the 138 subjects randomly assigned to treatment, 122 (88.4%) subjects completed the 28-day double-blind induction phase, and 16 (11.6%) subjects were withdrawn. A total of 77.8% patients in the ESK-NS+OAD, and 81.5% in the OAD + PBO-NS+ group received treatment on all eight dosing days. (18)

As described above TRANSFORM-3 evaluated the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (ESK-NS-56 mg or -84 mg + OAD) versus newly initiated OAD + PBO-NS in elderly population. (18)
During the double-blind induction phase of TRANSFORM-3, patients self-administered nasal spray treatment (esketamine or placebo) at treatment sessions twice per week for four weeks at the study site. The first nasal spray treatment session occurred on Day 1. On Day 1, patients randomised to receive esketamine nasal spray started on a dose of 28 mg in TRANSFORM-3. (18) At subsequent nasal spray treatment sessions in TRANSFORM-3, the dose could have been titrated as described in table 7.

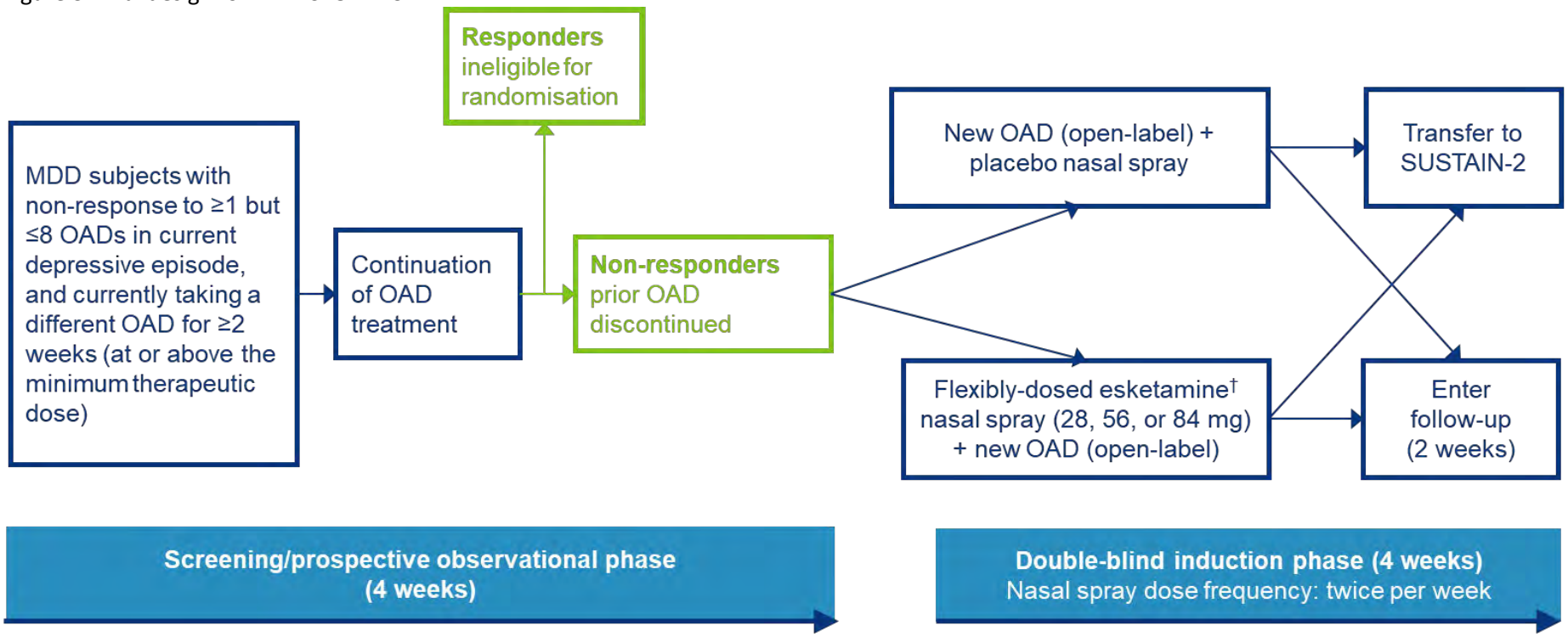
Table 7: ESK-NS dose titration schedule during the double-blind induction phase in the TRANSFORM-3 study. (18)

Study day	Esketamine dose	Dose titration guidance
TRANSFORM-3		
Day 1	28 mg	
Day 4	28 mg or 56 mg	The dose could remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability.
Days 8, 11, and 15	28 mg, 56 mg, or 84 mg	The dose could remain the same or increased or reduced by 28 mg from the previous dose, as determined by the investigator based on efficacy and tolerability. No dose increase was permitted beyond Day 15.
Days 18, 22, and 25	28 mg, 56 mg, or 84 mg	No dose increase was permitted beyond Day 15. If needed for tolerability, a dose reduction by 28 mg from the previous dose was permitted on Days 18, 22, and 25.

Dosing of the new OAD began on Day 1 of the induction phase of the TRANSFORM-3 and dosed was given as following (22):

- Duloxetin: The minimum therapeutic dose is 60 milligram per day (mg/day).
- Escitalopram: will be given at a dose of 10 mg/day throughout the Double-Blind Induction Phase. This dose (10 mg/day) is the also the minimum therapeutic dose.
- Sertraline: may be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 50 mg/day.
- Venlafaxine XR: may be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 75 mg/day.

Figure 3: Trial design for TRANSFORM-3



Abbreviations: MDD, major depressive disorder; OAD, oral antidepressant.
† On Day 1 of the induction phase, all patients randomised to receive esketamine nasal spray started with a dose of 28 mg. On Day 4, patients could either receive 28 or 56 mg. Thereafter, esketamine could be dosed flexibly (28, 56, or 84 mg) based on efficacy and tolerability up until Day 15 beyond which no dose increases were permitted. If needed for tolerability, dose reduction by 28 mg from the previous dose was permitted on Days 18, 22, and 25.
Note: Patients who withdrew early from the double-blind induction phase and received at least one dose of nasal spray study medication had an early withdrawal visit and then proceeded to the follow-up phase.

5.2.4 SUSTAIN-1

SUSTAIN-1 was a phase 3, double-blind, active-controlled, multicenter, relapse prevention study using a randomized withdrawal design in adults (18-64 years) with recurrent or single-episode TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) who have achieved stable remission or stable response after an induction and optimization course (16 weeks) of treatment with ESK NS + OAD.
SUSTAIN-1 consisted of an open-label induction phase (4 weeks; direct-entry patients only), an optimisation phase (12 weeks; both direct-entry and transferred-entry patients), and a double-blind maintenance phase. Transferred-entry patients from the OAD + PBO-NS arms of the acute ESK-NS trials (TRANSFORM-1 and TRANSFORM-2) were included in SUSTAIN-1 to maintain the blinding of the ongoing acute treatment trials and to capture safety data for OAD + PBO-NS beyond 4 weeks. (17) Schematic illustrating the study design of SUSTAIN-1 is presented in figure 4 at the end of this section. Furthermore, a detailed overview of the main study characteristics of SUSTAIN-1 is available at table A2.3.

The primary objective of this study was to assess the efficacy, safety and tolerability of flexibly doses ESK-NS + OAD (ESK-NS-56 or -84 + OAD) compared with an OAD (active comparator) + PBO-NS in delaying relapse of depressive symptoms in adult patients (18-64 years) with TRD who are in stable remission and response after an induction (4 weeks) and optimization (12 weeks) course of ESK-NS + OAD. Additionally, to investigate the safety and tolerability of ESK-NS + OAD compared with an OAD + PBO-NS. The primary efficacy endpoint was the time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable remission at the end of optimization phase after treatment with ESK-NS + OAD (based on MADRS). (17) The secondary efficacy endpoints are available at table A2.3.

A total of 1,097 patients were screened for SUSTAIN-1 of which 705 were enrolled (1):

- 437 direct-entry patients
- 268 transferred-entry patients from either TRANSFORM-1 or TRANSFORM-2

Transferred-entry patients who were on an OAD + PBO-NS were not included in efficacy analyses but were included in safety analyses. Of the patients who directly entered the open-label induction phase of SUSTAIN-1 and transferred-entry patients on ESK-NS + OAD, 455 met the criteria for response and started the optimisation phase.(1) Of the 455 patients who entered the optimisation phase, 176 met the criteria for stable remission and 121 met the criteria for stable response at the end of the optimisation phase and were therefore eligible to be randomised to receive treatment with either ESK-NS (flexibly-dosed: 56 or 84 mg) + OAD or OAD + PBO-NS during the maintenance phase. Of the 176 stable remitters 90 were randomized to receive ESK-NS + OAD and last 86 stable remitters were randomised to OAD + PBO-NS whereas 62 and 59 of the 121 stable responders were randomized to receive ESK-NS + OAD and OAD + PBO-NS, respectively. (17)

Further detailed description of the enrolled patients in SUSTAIN-1 from baseline to endpoint (up to 92 weeks) is described in table 8 (1):

Table 8: Enrolled patients in SUSTAIN-1

Phase	**Induction phase (4 weeks)**	**Optimization phase (12 weeks)**	**Maintenance phase (variable length)**
Patients enrolled	Of the 437 direct-entry patients, 273 (62.5%) subjects completed the 28-day induction phase and 164 (37.5%) subjects withdrew.	Of the 455 esketamine-treated subjects entering the optimization phase (including 182 esketamine-treated transferred-entry subjects), 297 completed the 12-week optimization phase and 158 (34.7%) subjects withdrew.	<u>Remitters</u> Of the 176 subjects in the Full (stable remitters) analysis set, 159 (90.3%) subjects completed the maintenance phase. (1) Median exposure to intranasal esketamine during the maintenance phase was 17.7 weeks in stable remitters and 19.4 weeks in stable responders.(17) <u>Responders</u> Of the 121 subjects in the Full (stable responders) analysis set, 113 (93.4%) subjects completed the maintenance phase. (1) Median exposure to placebo during the maintenance phase was 10.2 weeks among stable remitters and 10.1 weeks among stable responders.(17)

In general, the treatment groups were comparable with respect to baseline characteristics and an extensive overview of the baseline characteristics of patients is available in table A2.3a.
The mean (standard deviation [SD]) age of all subjects was 46.1 (11.10) years, ranging from 18 to 64 years. The majority of subjects entering the study were female (64.8%) and white (90.1%). In addition, the majority of subjects (62.9%) initiated OAD treatment with an SNRI and 46.2% of subjects received duloxetine. Medical history of hypertension was observed in 20.9% of subjects. The highest percentage of subjects was enrolled in the United States (27.0%), followed by Poland (18.7%), the Czech Republic (14.0%), Brazil (9.1%), and Turkey (7.5%); The mean (SD) baseline MADRS total score was 37.9 (5.50), ranging from 4 (1 subject, with a score >28 at screening with an unexpected significant score decrease on Day 1, who ultimately discontinued after the induction phase) to 53. Based on CGI-S scores, the majority of subjects (58.4%) were markedly ill (CGI-S score of 5). The mean (SD) duration of the current episode of depression was 132.2 (209.18) weeks (median 64.0 weeks). Subjects reported a family history of depression (45.1%), alcohol abuse (13.5%), and anxiety disorder (9.1%). A total of 27.4% of subjects had a history (lifetime) of suicidal ideation as assessed using the C-SSRS and 14.9% had a history of suicidal behavior. The mean (SD) IDS-C30 total score at screening was 47.2 (7.26), corresponding to severe depression. (1, 17)

As described above SUSTAIN-1 evaluated the efficacy, safety and tolerability of flexibly doses ESK-NS + OAD (ESK-NS-56 mg or -84 mg + OAD) compared with an OAD (active comparator) + PBO-NS. Regarding the details of the flexible dosage and frequency of nasal spray treatments during the open-label induction, optimisation, and maintenance phases, a detail description is outlined below. Note that no nasal spray study medication was administered during the screening/prospective observational or follow-up phases. (17)

Open-label induction phase

During the open-label induction phase, patients self-administered nasal spray treatment with esketamine (56 mg or 84 mg) at treatment sessions twice per week for four weeks as a flexible-dose regimen at the study site (17, 23). Dose titration was performed as described in table 9.

Table 9: ESK-NS dose titration schedule during the open-label induction phase of the SUSTAIN-1 study. (23)

Study day	Esketamine dose	Dose titration guidance
Day 1	56 mg	
Day 4	56 mg or 84 mg	The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability.
Days 8, 11, 15, 18, and 22	56 mg or 84 mg	The dose could remain the same or be increased to 84 mg (if the previous dose was 56 mg) or be reduced to 56 mg (if the previous dose was 84 mg) as determined by the investigator based on efficacy and tolerability.
Day 25	56 mg or 84 mg	A dose reduction from 84 mg to 56 mg was permitted if required for tolerability. No dose increase was permitted.

Optimisation phase

Transferred-entry patients continued the same double-blind nasal spray study drug (at the same dose) from the double-blind induction phase of TRANSFORM-1 or TRANSFORM-2. Direct-entry patients continued the same open-label ESK-NS treatment (at the same dose) from the open-label induction phase. (17)

During the optimisation phase, the MADRS was performed weekly by an independent, remote rater, and used to assign the frequency of nasal spray treatment sessions every four weeks. For all patients, the frequency of nasal spray treatment sessions was reduced from the twice weekly frequency used in the induction phase to weekly for the first four weeks of the optimisation phase (Week 5 to Week 8). (17)

Maintenance phase

All patients received double-blind nasal spray study drug during the maintenance phase. Patients were assessed weekly using the MADRS by an independent, remote rater, and treatment

administration frequency during the maintenance phase was based on an algorithm using the MADRS score and was reevaluated every 4 weeks, with nasal spray treatment self-administered either once weekly or every 2 weeks. (17)

OAD administration

Screening/prospective observational phase (direct-entry patients only)
At the start of the screening/prospective observational phase of the SUSTAIN-1 trial, direct-entry patients were already receiving an OAD with a documented non-response in their current episode of depression (on the basis of MGH-ATRQ). Patients continued to take this same OAD for four weeks to confirm non-response. Upon completion of four weeks of prospective treatment and assessment of OAD response, the OAD, if clinically indicated, could be tapered over a period of up to three weeks as per country-specific prescribing information. (17)

Open-label induction phase (direct-entry patients only)
Starting on Day 1, a new, open-label OAD was initiated in direct-entry patients and continued for at least the duration of the open-label induction phase. Doses were not to exceed the maximum doses as specified (23):

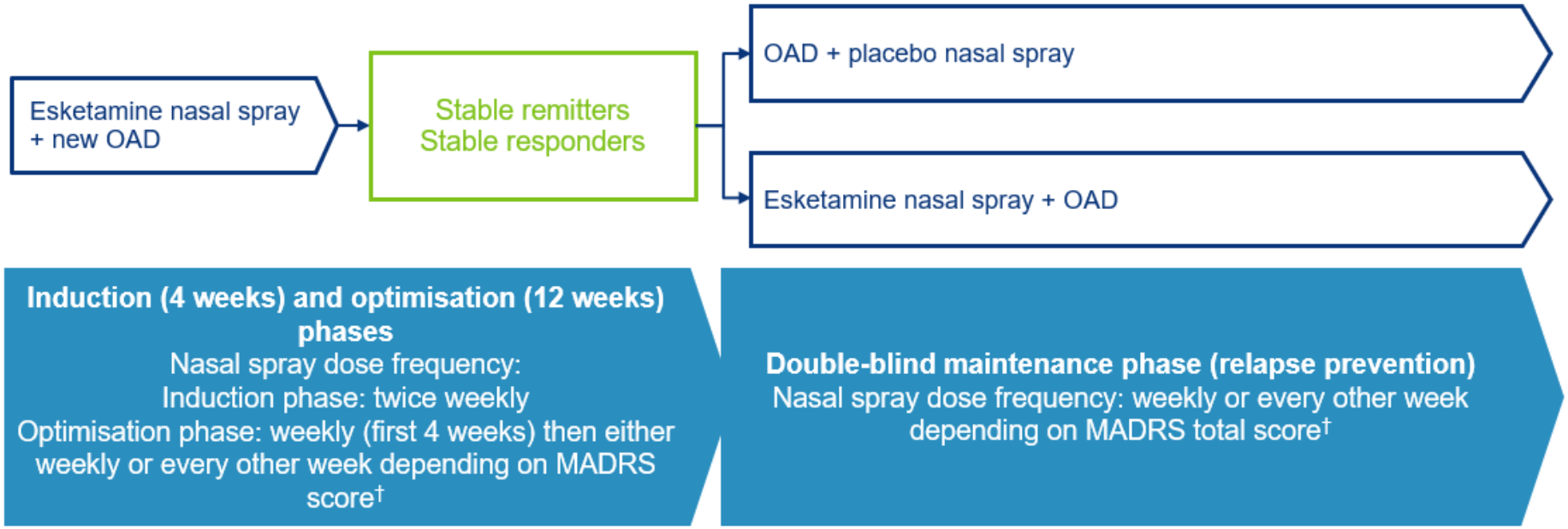
- Duloxetine: 60mg/day
- Escitalopram: 20 mg/day
- Sertraline: 200 mg/day
- Venlafaxine XR: 225 mg/day

If higher doses were not tolerated, a down-titration was permitted based on clinical judgment. However, the patient's dose was not to be lower than the following minimum therapeutic doses at the end of the induction phase (23):

- Duloxetine: 60 mg/day
- Escitalopram: 10 mg/day
- Sertraline: 50 mg/day
- Venlafaxine XR: 150 mg/day

Optimisation and maintenance phases
For both direct-entry and transferred-entry patients, the same OAD initiated on Day 1 of induction (the induction phase of TRANSFORM-1/2 in the case of transferred-entry patients) was continued throughout the optimisation and maintenance phase. The OAD dosage at the end of the induction phase was to remain unchanged. (17)

Figure 4: Trial design for SUSTAIN-1



Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, oral antidepressant; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray; TRD, treatment-resistant depression.
SUSTAIN-1 was a randomised, double-blind, long-term trial in adults (aged 18–64 years) with TRD who had achieved stable remission or stable response that compared the maintenance of efficacy of continued flexibly-dosed ESK-NS + OAD treatment with that of OAD + PBO-NS. The study ended upon 84 relapses occurring. An interim analysis was performed at 30 relapses. Efficacy analyses included direct-entry patient as well as patients transferred from TRANSFORM-1 and TRANSFORM-2 who were on ESK-NS + OAD and during these studies. Patients who were on OAD + PBO-NS during TRANSFORM-1 and TRANSFORM-2 could also enter the study but these patients were only considered in safety analyses. These patients were included in SUSTAIN-1 to maintain the blinding of the ongoing acute treatment trials, TRANSFORM-1 and TRANSFORM-2, and to capture safety data for OAD + PBO-NS beyond 4 weeks

5.2.5 SUSTAIN-2

SUSTAIN-2 was an open-label, multicenter, long-term study to evaluate the safety and efficacy of esketamine nasal spray plus a newly initiated oral AD in patients with TRD. Patients entered the study either directly (referred to as 'direct-entry patients') or after completing the double-blind induction phase of TRANSFORM-3, a short-term efficacy study in elderly patients with TRD (referred to as 'transferred-entry patients'). The trial was conducted at multiple centers in the US, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, France, Germany, Republic of Korea, Lithuania, Malaysia, Mexico, Poland, Romania, South Africa, Spain, Sweden, Taiwan, Turkey, and the UK. EMEA 48%, LATAM 21%, US 18%, APAC 13%, South Africa 8%, and Turkey 4%.(33, 34)

The primary objective of the SUSTAIN-2 trial was to assess the long-term safety and tolerability of ESK-NS + OAD with a particular focus on the following (33, 34):

- Potential effects on cognitive function
- Potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms
- Potential withdrawal and/or rebound symptoms following cessation of esketamine nasal spray treatment

Other safety and long-term efficacy outcomes of interest as part of the secondary objectives are outlined in table 10.

Table 10: Safety and Long-Term Efficacy Outcomes Measured as Part of the Secondary Objectives in SUSTAIN-2(33, 34)

Objective	Measurement
TEAEs	Local nasal tolerability
	Effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation,
	Effects on alertness and sedation
	Potential psychosis-like effects
	Dissociative symptoms
	Potential effects on suicidal ideation/behavior
Long-Term Efficacy	Depressive symptoms (clinician and self-reported), overall severity of depressive illness, functional impairment and associated disability, anxiety symptoms, and health related quality of life and health status
	Response rate over time, defined as: Percentage of patients with ≥50% reduction from baseline (induction phase) in the MADRS total score, Percentage of patients with ≥50% reduction from baseline (induction phase) in the PHQ-9 total score
	Remission rate over time, defined as: percentage of patients with MADRS total score ≤12, percentage of patients with PHQ-9 total score ≤5

The study consists of 4 phases: Screening Phase (4 weeks), Open-Label Induction Phase (4 weeks), Open-Label Optimization/Maintenance phase (48 weeks), and Follow up Phase (4 weeks). A schematic illustrating the study design of SUSTAIN-2 is presented in figure 5 at the end of this section and a detailed description of the four study phases is described in table 11. (33, 34)

Table 11: Trial Phases of SUSTAIN-2 (33, 34)

Trial Phase	Description
Screening Phase	• The 4-week screening phase for direct-entry patients provided adequate time to assess patient eligibility according to the study entry criteria • Transferred-entry patients from TRANSFORM-3 study would not participate in the 4-week screening phase • Direct-entry patients were eligible for screening regardless of whether or not they were currently taking oral AD treatments. At screening, patients must have had a nonresponse to ≥2 different oral AD treatments in the current MDE, as assessed by MGH-ATRQ criteria and confirmed by documented medical history and/or prescription/pharmacy records • Patients taking AD medication(s) at the start of the screening phase discontinued their current AD treatment prior to the start of the induction phase. If clinically indicated, the AD medication(s) could either be tapered and discontinued during the screening phase, or discontinued and switched directly to 1 of the 4 new oral AD medication(s) available in the trial on Day 1 of the open-label induction phase, per clinical judgment • Patients not currently taking oral AD medication(s) at screening would start 1 of the 4-selected new oral AD medication (duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]) on Day 1 of the open-label induction phase
Open-Label Induction Phase	• The 4-week open-label induction phase for direct entry patients was selected based upon the onset of effect of typical ADs, with a 4-week duration considered to be sufficiently long to show the AD effects of the active comparator • For direct-entry patients esketamine nasal treatment was twice weekly for 4 weeks. Patients who were <65 years old would start with initial dose of 56 mg on Day 1, with the dose adjusted based on efficacy and tolerability in the subsequent visits of the induction phase, (flexible dose: 56 mg or 84 mg). Patients who were <65 years old would start with an initial dose of 28 mg on Day 1, titrated to 56 mg on Day 4, with the dose adjusted based on efficacy and tolerability (either 56 or 84 mg) in the subsequent visits of the induction phase. In addition, all direct-entry patients would initiate a new, open-label oral AD on Day 1, which will be taken daily during the study • For transferred-entry non-responder patients from TRANSFORM-3, these patients would start with an initial dose of 28 mg on Day 1, titrated to 56 mg on Day 4, with the dose adjusted based on efficacy and tolerability (either 56 or 84 mg) in the subsequent visits of the induction phase. These patients would continue taking the same oral AD at the same dose as taken in the last week of the double-blind induction phase of TRANSFORM-3 • If a participant withdrew from the study before the end of the open-label induction phase for reasons other than withdrawal of consent, an early withdrawal visit should be conducted followed by the follow-up phase

Trial Phase	Description
Optimization/ Maintenance Phase	• The duration of 48 weeks for the optimization/maintenance phase for both direct-entry and transferred-entry patients allowed for a reduction in the frequency of nasal spray treatment sessions and subsequent individualization and stabilization of the treatment session frequency (weekly or every other week) for a given participant (using the MADRS total score to assess depressive symptoms) • Responder patients at the end of the induction phase of SUSTAIN-2, was eligible to proceed to the optimization/maintenance phase; and continue receiving open-label esketamine nasal spray treatment (at the same dose; 56 mg or 84 mg) and the same oral AD medication(s) (at the same dose) as taken in the last week of the induction phase of SUSTAIN-2 • Non-responders at the end of the induction phase of the current study would complete an early withdrawal visit and proceed to the follow-up phase • Eligible transferred-entry responder patients from TRANSFORM-3 would join the current study starting from the optimization/maintenance phase. These patients would all start with an initial dose of 28 mg (Week 5; Study Day 32) and have their dose adjusted over the following 3 weeks of the optimization/maintenance phase. Patients would continue to take the same oral AD (at the same dose) that they received at the end of the induction phase of TRANSFORM-3 • For all patients, the nasal spray treatment session frequency would be reduced from that in the induction phase (twice weekly) to weekly for the first 4 weeks of the optimization/maintenance phase (i.e., Week 5 to Week 8). After the first 4 weeks, the frequency of nasal spray treatment sessions would be adjusted to once weekly or once every other week based on the severity of depressive symptoms, as assessed by the MADRS total score. A maximum of 3 changes in nasal spray treatment session frequency from weekly to every other week was permitted during the optimization/maintenance phase • If a participant withdrew from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, an early withdrawal visit would be conducted, followed by the follow-up phase
Follow-Up Phase	• The 4-week duration of the follow-up phase allowed sufficient time to assess safety and tolerability after cessation of nasal spray dosing • This phase included all patients who received at least 1 dose of nasal spray study medication in this study. Follow up visits would be performed at 1, 2 and 4 weeks after the last dose of nasal spray study drug • At the start of the follow-up phase, further clinical/standard of care for the treatment of depression was arranged by the study investigator and/or the participant's treating physician. Patients would be provided with an additional 4-week supply of the oral AD medication to ensure that there is no interruption of oral AD therapy during the transition to further clinical/SoC

A total of 1.616 subjects were screened for SUSTAIN-2 of 802 subjects were enrolled in this study, see table 12. Of these subjects, 691 were direct-entry subjects, and 111 were transferred-entry subjects from the TRANSFORM-3 study.(33)

Of the 802 subjects enrolled, 364 subjects were treated for 6 months and 136 subjects for 12 months. A total of 178 subjects were ≥65 years of age, and 19 subjects were ≥75 years of age.(33)

Of the 779 subjects who entered the induction phase (that included 88 non-responders from the TRANSFORM-3 study), most subjects (74.5%; 580 subjects) continued to the optimization/maintenance Phase, see table 13. The main reasons for withdrawal during the induction phase were: 1) subject does not meet criteria
for continuing into the next phase (i.e., non-responders in the induction phase) (10.8%) and 2) due to adverse event (6.7%).(33)

A total of 603 subjects entered the optimization/maintenance phase (580 from the induction phase and 23 responders from the TRANSFORM-3 study, see table 13. Approximately 25% of subjects completed the optimization/maintenance phase (24.9%; 150 subjects). Because the study completion specification was met for number of subjects exposed for 6 months and 12 months, a large percentage of subjects (54.9%) did not complete the full duration of the optimization/maintenance phase. A total of 453 subjects (75.1%) withdrew from the phase with the main reasons for withdrawal being: 1) study terminated by sponsor (i.e., due to predefined total subject exposure criteria) (54.9%); 2) withdrawal by subject (5.0%); 3) lack of efficacy (4.1%); 4) adverse event (4.1%); and 5) other (3.5%).(33)

A total of 357 of 802 subjects entered the follow-up phase, and 91.3% (326 of 357 subjects) of subjects completed this phase.(33)

Table 12: Numbers of direct- and transferred-entry patients in SUSTAIN-2

	ESK-NS + OAD (N=802)
Direct-entry patients, n (%)	691 (86.2)
Transferred-entry patients from TRANSFORM-3, n (%)[a]	111 (13.8)
Non-responder patients:	88 (11.0)
Esketamine 28 mg + OAD	3 (0.4)
Esketamine 56 mg + OAD	9 (1.1)
Esketamine 84 mg + OAD	28 (3.5)
OAD + placebo	48 (6.0)
Responder patients:	23 (2.9)
Esketamine 28 mg + OAD	1 (0.1)
Esketamine 56 mg + OAD	5 (0.6)
Esketamine 84 mg + OAD	9 (1.1)
OAD + placebo	8 (1.0)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; OAD, oral antidepressant.
[a] For transferred-entry patients, the final esketamine dose in TRANSFORM-3 is presented.

Table 13: Numbers of patients in each phase and analysis set in SUSTAIN-2

Analysis set, n (%)	ESK-NS + OAD (N=802)
Open-label induction phase	
Full (IND)	779 (97.1)
Optimisation/maintenance phase	
Full (OP/MA)	603 (75.2)
Follow-up phase	
Follow-up	357 (44.5)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction; OP/MA, optimisation/maintenance phase.

A higher percentage of subjects were women (62.6%) and white (85.5%). The median age was 53.5 years (range: 18 to 86 years). Elderly subjects (≥65 years) made up 22.2% (178) of subjects. The mean (SD) weight was 78.51 (18.426) kg, with 256 subjects who were either obese (28.4%) or morbidly obese (3.5%). A similar percentage of subjects received either SNRIs or SSRIs as the oral antidepressant initiated on Day 1. Of the subjects in this study, approximately 40% of subjects were not responsive to 3 or more antidepressant medications during the current episode. Mean (SD) MADRS total score was 31.4 (5.39) at baseline. Based on the C-SSRS, 26.9% of subjects reported suicidal ideation within the past 6 months, and 27.4% of subjects reported a medical history of hypertension. Subject enrollment was highest in the United States (18.3%), followed by Argentina (13.2%), Bulgaria (11.7%), Sweden (11.2%), South Africa (8.0%), Brazil (6.5%), and Spain (5.2%).(33) Furthermore, a detailed overview of the main study characteristics of SUSTAIN-2 is available at table A2.4.(33)

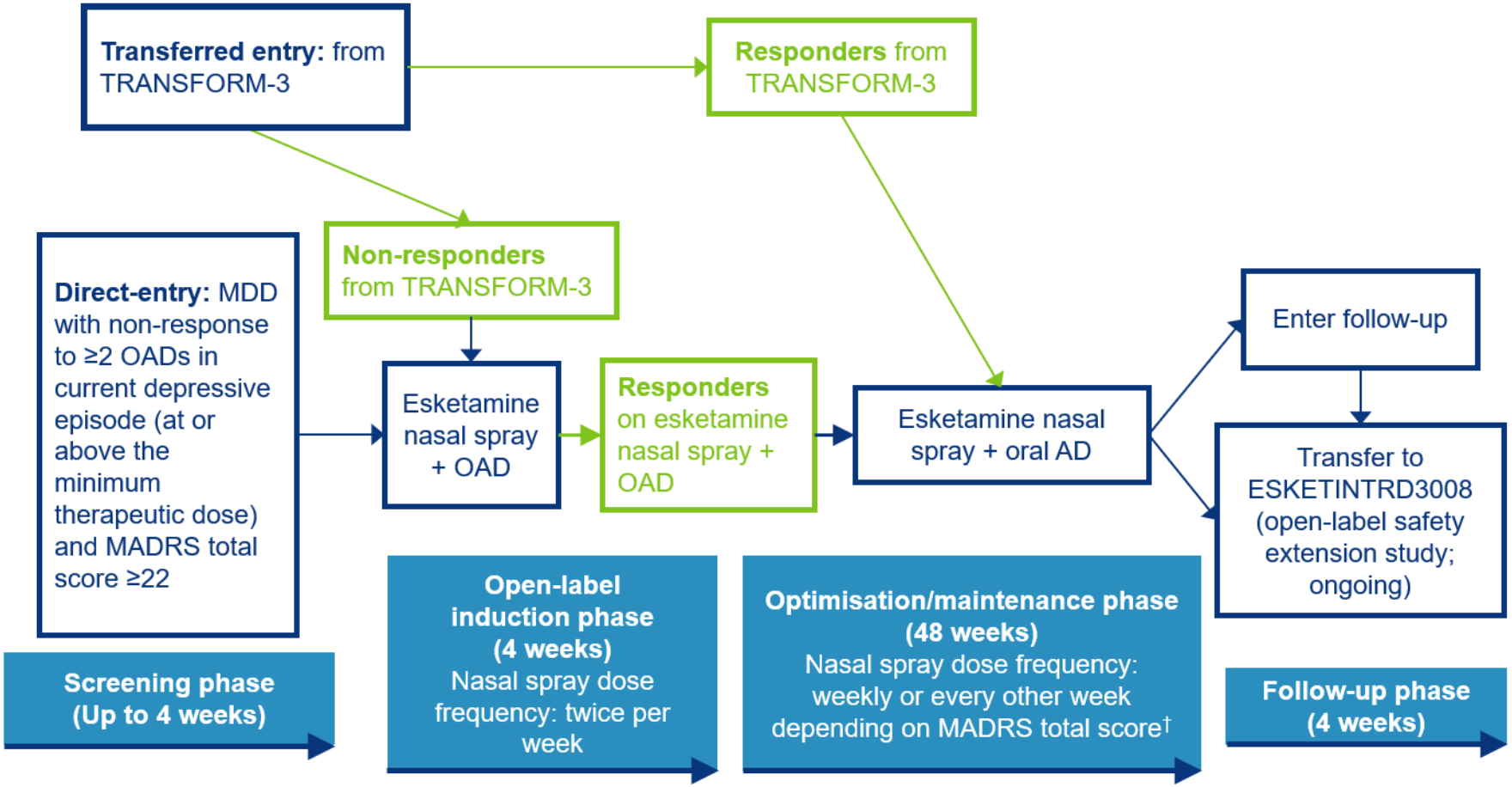
Treatment Regimen

Patients who entered the 4-week induction phase of SUSTAIN-2 having completed the TRANSFORM-3 study received esketamine nasal spray (56 mg or 84 mg) and the same oral AD as they were currently using, while those entering the trial directly were given a new oral AD treatment in conjunction with esketamine nasal spray. (33, 34)

In the optimization/maintenance phase lasting 48 weeks, patients took a dose of esketamine nasal spray according to their age (56 mg or 84 mg for those <65 years; 28 mg, 56 mg or 84 mg for those ≥65 years), with those transferring from the TRANSFORM-3 study taking the 28 mg dose for the first week before taking the dose suitable based on response thereafter. All patients continued taking the same AD in this phase. From weeks 9 to 52 of the optimization/maintenance phase, esketamine nasal spray was dosed either weekly or every other week depending on the MADRS score with the aim of having the lowest frequency to sustain remission. Switching to every other week treatment (if total MADRS score was ≤12) or back to weekly treatment (if total MADRS score was >12) was possible at 4-week intervals, starting at week 8. (33, 34)

The maximum duration of treatment will be 60 weeks for direct-entry patients, 56 weeks for transferred-entry non-responder patients, and 52 weeks for transferred-entry responder patients. The end of the study will occur when at least 300 patients have received treatment with nasal spray esketamine for 6 months and at least 100 patients for 12 months (Note: the total number of patients will be based on patients from this study and patients from other esketamine nasal spray Phase III studies). (33, 34)

Figure 5: Trial design for SUSTAIN-2 (33, 34)



Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAD, oral antidepressant.
Note: At entry to SUSTAIN-2, transferred-entry patients were to continue to receive the same OAD initiated in TRANSFORM-3. A new OAD medication was only initiated for direct-entry patients. Only responders from the induction phase were eligible to continue to the optimisation/maintenance phase. The non-responders from the induction phase had the option of entering the follow-up phase. Patients were able to enter the open-label safety extension study SUSTAIN-3 (ongoing) at any time during SUSTAIN-2.

5.2.6 SUSTAIN-3

SUSTAIN-3 is an ongoing phase III, multicenter, open-label, long-term extension study to evaluate the safety, tolerability, and efficacy or esketamine nasal spray in patients with TRD. The trial is conducted in multiple centers in the US, Belgium, Canada, Germany, Hungary, Republic of Korea, Malaysia, Poland, Spain, Sweden, Taiwan, Turkey, and the UK. Patients from all previously described phase III trials (TRANSFORM-1, -2 and -3, and SUSTAIN-1 and -2) were eligible for enrolment.(24, 25)

The primary objective of SUSTAIN-3 was to assess the long-term safety of esketamine in conjunction with oral ADs in patients with TRD as detailed in table A2.5. TEAEs of special interest were analyzed separately, with those of particularly interest including increased blood pressure, increased heart rate, transient dizziness/vertigo, an impaired cognition, anxiety, and lower urinary tract symptoms including cystitis. Other objectives included the assessment of long-term efficacy including effects on depressive symptoms, severity, functioning and associated disability, HR-QoL, and to ensure access to esketamine nasal spray for those patients until it becomes commercially available The primary and secondary outcome measures of SUSTAIN-3 were safety outcomes, as detailed in table 14.(24, 25)

Table 14: Efficacy, Safety and Exploratory Endpoints for SUSTAIN-3(24, 25)

	Criteria	
Primary Outcomes	Occurrence of TEAEs	Including TEAEs of special interest
	Potential short-term effects observed on the day of nasal spray treatment session with special attention to changes from baseline/pre-dose over time	Blood pressure (systolic and diastolic) and heart rate Blood oxygen saturation 12-lead ECG Alertness and sedation using MOAA/S
	Long-term effects, with special attention to changes from baseline over time	CCB and HVLT-R, to assess potential effects on cognitive function C-SSRS to assess potential effects on suicidal ideation and behavior
	Changes from baseline over time in clinical laboratory tests	Including hematology, serum chemistry, and urinalysis
	Change in time to discharge readiness, using CGADR	Time to discharge readiness Using the Clinical Global Assessment of Discharge Readiness
Efficacy Outcomes	Change in number of responders and remitters as measured by MADRS total score and PHQ-9 total score	Response (≥50% improvement from baseline) and remission (MADRS total score ≤12, PHQ-9 total score <5)
	Overall severity of illness, using CGI-S	Change from baseline in severity of depression as assessed with the CGI-S score

	Change in functioning and associated disability as measured by SDS total score	Change from baseline in patient-reported functioning and associated disability as assessed by the SDS total score at end of double-blind induction phase
	Change in HR-QoL and health status as measured by EQ-5D-5L	Change from baseline in patient-reported health-related quality of life and health status as assessed by EQ-5D-5L
	Change in HR-QoL as measured by QLDS	Change from baseline in patient-reported health-related quality of life as assessed by QLDS

Abbreviations: CGADR: Clinical Global Assessment of Discharge Readiness; CGI-S; Clinical Global Impression-Severity; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: Electrocardiogram; EQ-5D-5L: European Quality of life group 5-Dimension-5 Level; HVLT-R: Hopkins Verbal Learning Test-Revised; MAGDA: Magda Avatar Game Depression implicit Association; MADRS: Montgomery Åsberg Depression Rating Scale; MOAA/S: Modified Observer's Assessment of Alertness/Sedation; QLDS: Quality of Life in Depression Scale; PHQ-9: Patient Health Questionnaire-9; SDS: Sheehan Disability Scale; TEAE: Treatment-emergent adverse event

SUSTAIN-3 consist of two distinct phases i.e. the induction phase and optimization/maintenance phase. In the induction phase, patients will receive esketamine nasal spray treatment twice a week for 4 weeks. At the end of this 4-week period, those defined as responders (defined as ≥50% reduction in the MADRS total score from baseline) are eligible to proceed to the optimization/maintenance phase. In the optimization/maintenance phase, dosages can be altered according to patient response and physician discretion. Patients who are currently in the optimization/maintenance phase at the time SUSTAIN-3 is completed will conduct an "End of Study" visit as their final study visit within 1 week of the last nasal spray dose. (24, 25)

The optimization/maintenance phase is of variable length, with study participants being stopped (24):

- At the end of December 2020 or when esketamine nasal spray is commercially available in the subject's respective country (whichever is later); or
- The subject no longer benefits from further treatment (based on the investigator's clinical judgment), or withdraws consent; or
- The clinical development of esketamine nasal spray for TRD in that country/region is terminated

A schematic illustrating the study design of SUSTAIN-3 is presented in figure 6 at the end of this section.

As described above, the cohort selected for SUSTAIN-3 was comprised of patients who had completed any of the other Phase III esketamine trials. Table 15, outlines the eligibility of patients that were enrolled in the other esketamine trials who were then eligible for enrollment in SUSTAIN-3.

Table 15: SUSTAIN-3 Entry Points for Patients from Previous Studies

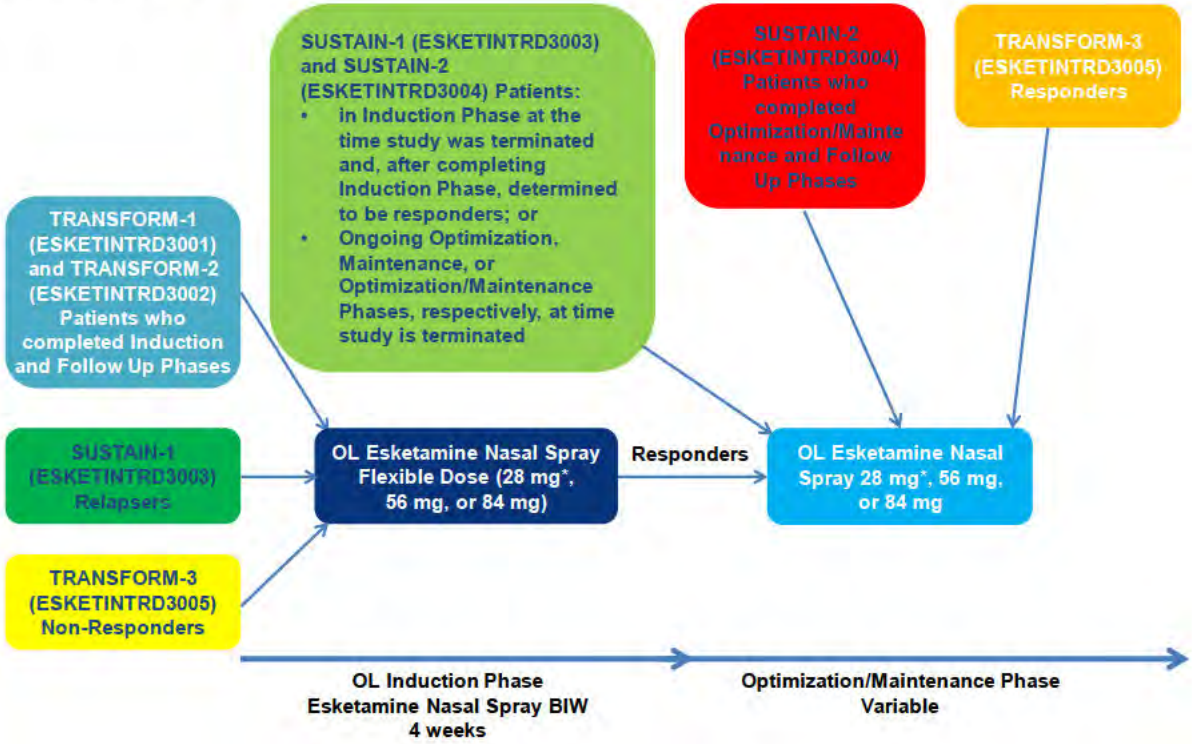
Prior Study	Inclusion Requirement	Point of Entry for SUSTAIN-3
TRANSFORM-1	Subject completed induction phase and 6-month follow-up phase	Induction phase
TRANSFORM-2	Subject completed induction phase and 6-month follow-up phase	Induction phase
TRANSFORM-3	Subject was in the induction phase of TRANSFORM-3 study at the time enrollment into the SUSTAIN-2 study was closed and, after completion of the induction phase, was determined to be a responder	Optimization/maintenance phase
	Subject was in the induction phase of TRANSOFRM-3 study at the time enrollment into the SUSTAIN-2 study was closed and, after completion of the induction phase, was determined to be a non -responder.	Induction phase
SUSTAIN-1	Subject relapsed in maintenance phase	Induction phase
	Subject was in the induction phase at the time the study was terminated and, after completion of the induction phase, was determined to be a responder	Optimization/maintenance phase
	Subject was in the optimization or maintenance phase at the time the study was terminated	Optimization/maintenance phase
SUSTAIN-2	Subject completed the optimization/maintenance phase and follow-up phase	Optimization/maintenance phase
	Subject was in the induction phase at the time the study was terminated and, after completion of the induction phase, was determined to be a responder	
	Subject was in the optimization/maintenance phase at the time the study was terminated	

[redacted]

Treatment Regimen

In the open-label induction phase participants will self-administer with esketamine nasal spray twice per week for 4 weeks as a flexible dose regimen (56 milligram [mg] or 84 mg for those < 65 years; 28 mg, 56 mg or 84 mg for those >= 65 years). Participants >= 65 years old will start at a dose of 28 mg on Day 1. In the optimization/maintenance phase, participants entering from studies TRANSFORM-1, TRANSFORM-2, SUSTAIN-1, SUSTAIN-2, or ESKETINTRD3006 (US sites only) will self-administer esketamine nasal spray (same dose) once weekly. Participants entering from TRANSFORM-3 will self-administer esketamine nasal spray (28 mg in week 1; 28 or 56 mg in week 2; and 28, 56 or 84 mg in week 3 and 4) once weekly. After Week 4 (starting at Week 5), based on the Investigator's clinical judgment, the dose of esketamine for all participants can be adjusted based upon efficacy and tolerability.(24, 25)

Figure 6: SUSTAIN-3 Trial Design (24, 25)



5.2.7 SYNAPSE

SYNAPSE was a Phase IIa doubly-randomized, double-blind, placebo-controlled, multicenter study of esketamine nasal spray for the treatment of patients with moderate to severe MDD who failed to respond to at least 2 AD therapies during their current MDD episode (History of inadequate response to ≥2 ADs of which ≥1 AD was used in the current episode of depression). It should be noted that this inclusion criteria differs from the TRD definition as well as the population studied in the Phase III trials.(26, 27)

The primary objective of SYNAPSE was to evaluate the efficacy, and dose response of esketamine nasal spray patients with TRD compared with placebo nasal spray. The primary endpoint of SYNAPSE was the change from baseline in MADRS total score at the final day. The primary and key secondary outcome measures are described in table 16. (26, 27)

Table 16: Primary and Key Secondary Outcome Measures in SYNAPSE (26, 27)

	Outcome Measure	Description
Primary Outcome	Change in depressive symptoms as measured by MADRS total score	Change from baseline to day 8 in each period in MADRS total score
Secondary Outcomes	Response as measured by MADRS total score	Defined as at least 50% improvement from baseline in the MADRS total score with an onset by day 2 that is maintained to study day 15
	Change in number of responders as measured by MADRS total score	Number of patients who experience a 50% or greater improvement in their MADRS score from the day 1 to study day 15

The trial was conducted in two panels, Panel A was conducted in 10 sites in the US and 1 site in Belgium, and Panel B was conducted in 11 sites in Japan only. As such, this dossier will focus only on the design and results of Panel A. (26, 27) The SYNAPSE trial consisted of four discrete phases, as described in table 17.

Table 17: Trial Phases for SYNAPSE (26, 27)

Trial Phase	Description
Screening Phase	Prospective assessment of treatment response to the patient's current oral AD across 4 weeks. Non-responders were eligible to proceed to the double-blind induction phase, patient to additional eligibility criteria
Double-Blind Treatment Phase	Patients entering the double-blind treatment induction phase ceased their current AD therapy, and began esketamine nasal spray for a 2-week treatment phase composed of two treatment periods
Open-Label Treatment Phase (optional)	Patients entering the optional open-label treatment phase received esketamine nasal spray from day 15 to day 74
Follow-Up Phase	All patients were entered into an 8-week follow-up phase regardless of their inclusion in the open-label phase

During the double blind treatment phase, patients received esketamine nasal spray or placebo nasal spray in two dosing periods; period 1 included dosing days 1 and 4, and period 2 included dosing days 8 and 11. In period 1, patients were randomly assigned 3:1:1:1 to receive placebo nasal spray, esketamine nasal spray 28 mg, esketamine nasal spray 56 mg, or esketamine nasal spray 84 mg, respectively. (26, 27)

In period 2, patients initially assigned to placebo nasal spray were reassigned based on their QIDS-SR_{16} (Quick Inventory of Depressive Symptomatology [Self-Report] 16 item) total score, if they had mild or no depressive symptoms (QIDS-SR_{16}<11) received the placebo, or if they had moderate to severe symptoms (Moderate [QIDS-SR_{16}=11-16]; Severe [QIDS-SR_{16}>16]) were randomly assigned 1:1:1:1 to receive placebo nasal spray, esketamine nasal spray 28 mg, esketamine nasal spray 56 mg, or esketamine nasal spray 84 mg, respectively. In the optional open label treatment phase, all patients who entered received esketamine nasal spray from day 15 to day 74, at a starting dose of 56 mg which was titrated up to 84 mg, with a post-study treatment follow-up of 8 weeks. An overview of the treatment arms used in the SYNAPSE trial is illustrated in figure 7 at the end of this section. (26, 27)

SYNAPSE enrolled patients with moderate to severe MDD who had experienced an inadequate response to at least one AD therapy during their current depressive episode. The key inclusion and exclusion criteria for the SYNAPSE trial population are provided in table 18. (26, 27) Furthermore, a detailed overview of the main study characteristics of SYNAPSE available at table A2.6.

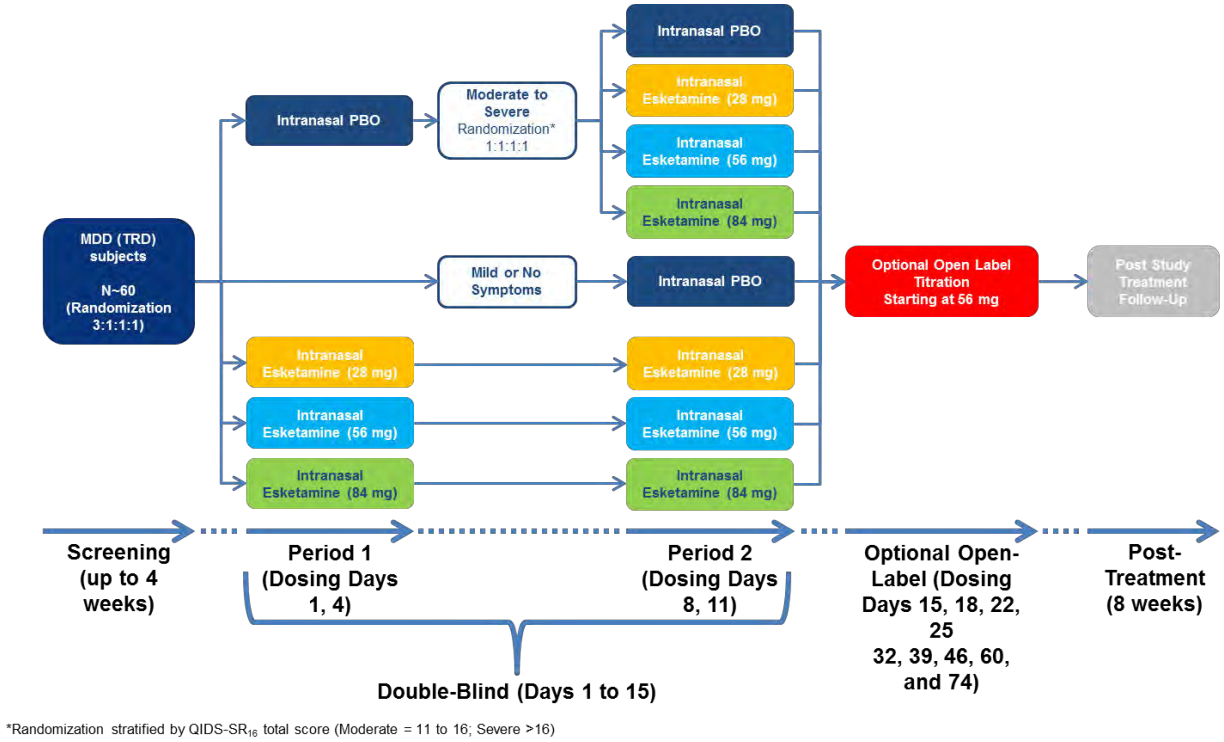
Table 18: Key Eligibility Criteria for SYNAPSE. (26, 27)

Criteria	Description
Inclusion Criteria	Males and females aged 20 years to 64 years
	Diagnosed with MDD without psychotic features as per DSM-IV-TR diagnostic criteria
	Confirmed diagnosis of moderate to severe depression (defined as IDS-C30 total score ≥34 at screening and pre-dose at day 1)
	≥1 failed ADs in current major depressive episode in addition to 1 in previous episodes
Exclusion Criteria	Current diagnosis of bipolar and related disorders, intellectual disability, or cluster b personality disorder
	Current or prior diagnosis of a psychotic disorder, MDD with psychosis, PTSD, OCD, anatomical or medical conditions that may impede delivery or absorption of study medication
	Abnormal or deviated nasal septum with any 1 or more of the following symptoms: blockage of 1 or both nostrils, nasal congestion (especially 1-sided), frequent nosebleeds, frequent sinus infections, and at times has facial pain, headaches, and postnasal drip
	Has a history of substance abuse or dependence within the previous 1 year of the screening visit
	Known allergies, hypersensitivity, intolerance, or contraindication to esketamine/ketamine or its excipients

Abbreviations: DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders -Fourth Edition-Text Revised; IDS-C30: Inventory of Depressive Symptomatology-Clinician; MDD: Major depressive disorder; MDE: Major depressive episode; MINI: Mini-International Neuropsychiatric Interview; OCD: Obsessive compulsive disorder; PTSD: Post-traumatic stress disorder.

A total of 126 individuals were screened, 67 of whom met the eligibility criteria and were randomized. Overall for panel A, 63 patients (94.0% of those enrolled) completed period 1, and 60 patients (89.6%) completed the 2-week double-blind study phase (periods 1 and 2). Of the 28 patients assigned to placebo nasal spray who were eligible for re-randomization at the end of period 1, 27 (96.4%) went on to complete period 2. Of these completers, 57 entered the open-label phase, with 51 (89%) subsequently entering the follow-up phase, 41 (80%) of whom completed the week 8 follow-up visit. (26, 27)

Figure 7: SYNAPSE Trial Design (26, 27)



Abbreviations: MDD; Major depressive disorder, mg; Milligrams, N; Number, PBO; Placebo, wks; Weeks; TRD: Treatment-resistant depression

5.2.8 ATU

The French National Agency for Medicines and Health Product Safety (ANSM) granted on August 2nd 2019 a "cohort" Temporary Authorization for Use (ATUc) for ESKETAMINE JANSSEN 28 mg, nasal spray for the following indication: "ESKETAMINE JANSSEN is indicated for adults with treatment-resistant Major Depressive Disorder who have not responded to at least two different treatments with antidepressants of two different classes in the current moderate to severe depressive episode with contraindication to electroconvulsive therapy (ECT), without access to ECT, resistant to ECT, or who refuse ECT. ESKETAMINE JANSSEN must be co-administered with a newly initiated oral antidepressant."(28, 35-37) Furthermore, a detailed overview of the main study characteristics of ATU available at table A2.7.

A first report dated January 31st, 2020 was submitted to ANSM on February 4th, 2020, covering data collected from September 23rd, 2019 to January 3d, 2020.(38) However, this dossier will present data based on the second report including complete data collected over the cumulative period from September 23rd, 2019, to March 25th, 2020.(28, 35)

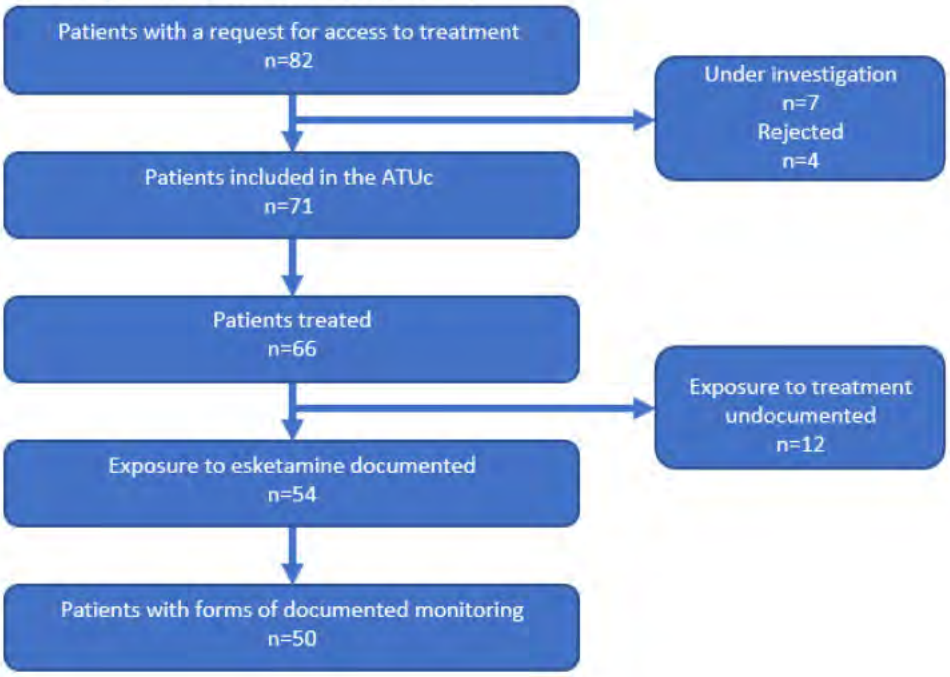
The eligibility criteria of the cohort ATU were as follows(28, 35-37):

- Male or Female older than 18 years old
- Patient with moderate to severe depression based on clinical judgement
- Patient with a diagnosis of treatment-resistant depression without other therapeutic alternatives:
    - Meeting the DSM-5 diagnostic criteria for a single episode of major depression (if it is a single episode, the duration must be at least 2 years) or a recurrent episode with no psychotic features
    - Non-response to at least two different classes of antidepressant medications during the current depressive episode confirmed by medical history and have a contraindication to electroconvulsive therapy (ECT), be resistant to ECT, no access to ECT or refuse ECT
- Patient medically stable based on physical examination, medical history and vital signs (including stable blood pressure)
- Not being able to take part of a clinical trial
- Before starting treatment, women of childbearing potential should use a highly effective method of contraception and agree to continue to use it for the duration of the ATU and for at least six weeks after the last dose of esketamine

From September 23rd 2019 to March 25th 2020, eighty-two (82) treatment-access-request forms were received, see figure 8. Among those eighty-two (82) treatment access request forms (28, 35-37):

- Seventy-one (71) 71 requests for access to treatment were approved
- Seven (7) were still under investigation at the ATUc end date, March 25th, 2020, and were not included in the ATUc.
- Four (4) were rejected due to treatment access criteria not met: two (2) patients presented bipolar disorder, one (1) presented psychotic disorder and one (1) patient had an history of aneurysm.

Figure 8: patient flow in ATU (28, 35-37)



Administration

The eligible patients received esketamine according to the Summary of Product Characteristics , in association with a newly initiated oral anti-depressant, see table 19 (28, 36, 37):

- The administration took place at the hospital.
- Each patient was monitored after administration for ≥ 120 minutes by a healthcare professional according to the recommendations of the SPC.

Table 19: ESK-NS dose schedule for the ATUc. (28, 36, 37)

Patient age	**Esketamine dose**			
	Initial dose	Subsequent doses	Weeks 5-8	Weeks 9+
≥18-<65 years	56 mg	56 mg or 84 mg twice a week	56 mg or 84 mg once a week	56 mg or 84 mg every 2 weeks or once a week
≥65 years	28 mg	28 mg, 56 mg or 84 mg twice a week	28 mg, 56 mg or 84 mg once a week	28 mg, 56 mg or 84 mg every 2 weeks or once a week

5.2.9 TRD cohort study

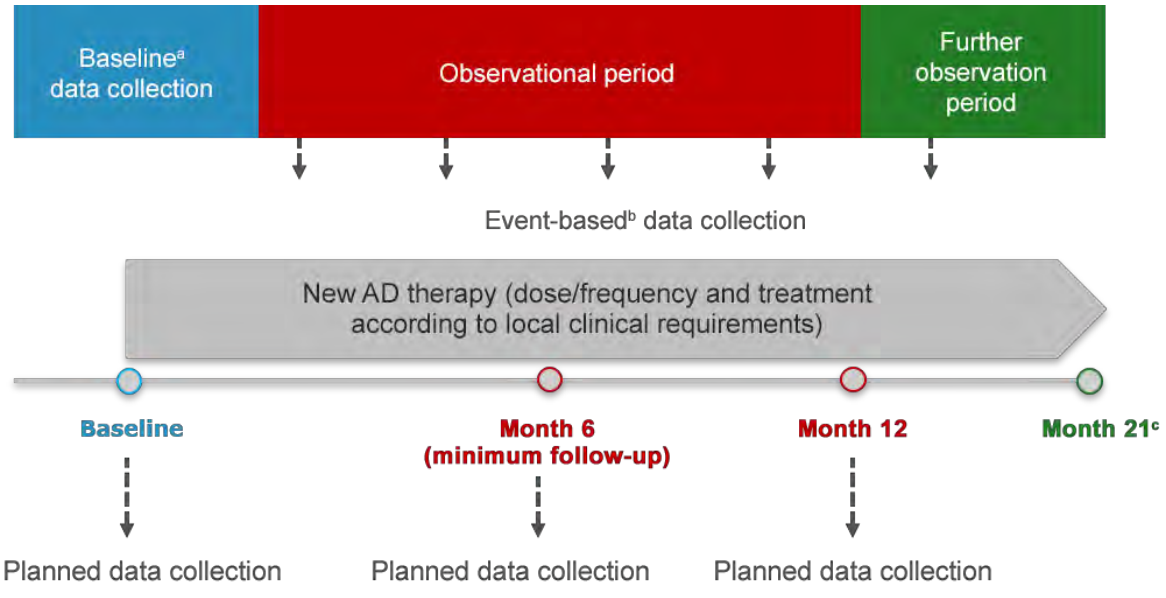
Study design

The therapy-resistant depression (TRD) cohort in Europe (hereinafter prospective TRD cohort study or TRD cohort) is a multicentre, non-interventional, prospective cohort study with 411 patients with therapy-resistant major depression from Europe (Belgium, Germany, Italy, the Netherlands, Portugal, Spain, the United Kingdom (UK)), who are being treated with a newly-initiated oral antidepressant (AD). The patients will be observed for at least 6 months to a maximum of 21 months (6 months after the last patient is admitted). The objective of the study is to collect clinical data in the demographic treatment routine, the disease burden including the use of health resources in patients with TRD who are treated in Europe with the current standard treatment. The collection includes data on socio-demographic and disease-related characteristics, social and economic burden (i.e. health-related quality of life, loss of work productivity, impairment of daily functioning), naturalistic therapy regimens and other treatment methods, the associated clinical findings and the use of health resources.(29, 30, 39)

Study duration

The study starts with a data collection at baseline, which is followed by a 6 to 12 month observation phase, an extended observation phase up to a maximum of 6 months after the inclusion of the last patient, see figure 9.(29)

Figure 9: Study design for the Treatment-Resistant Depression Cohort in Europe study. (29)



a: Baseline values were documented on the day of the start of a new treatment ±14 days
b: Any clinically relevant improvement/deterioration in the current episode of the disease
c: 21 months was the maximum time in the study of a patient; all patients had at least 6 months of follow-up
Abbreviations: AD: Antidepressant, TRD: Therapy-resistant Major Depression

Study population

The TRD cohort includes subjects who (29, 30, 39):

- are ≥18 years old
- meet the diagnostic criteria for a single episode of MDD or recurrent MDD without psychotic symptoms
- meet the TRD criteria, defined as the absence of a clinically significant improvement (≤ 25% improvement in the MADRS total score) with at least two different oral AD treatments in the current episode of depression, administered in adequate doses (defined by the MGH-ATRQ) with moderate to severe depressive major depression defined by the total score of the Montgomery-Åsberg Depression Rating Scale (MADRS) ≥ 20 (prospective TRD cohort study)

The final analysis set consisted of 411 subjects who were distributed across seven European countries. Of the seven European countries, Italy presented the highest proportion of patients in the cohort (30.2%) followed by Spain (17.3%), Germany (14.4%), UK (11.9%), Belgium (10.7%), Portugal (9.0%) and Netherlands (6.6%). The mean (SD) age of patients was 51.0 (10.8) years and 62.3% were female, however the populations mean (SD) age at diagnosis of MDD was 37.2 (13.1) years. Consequently, the diagnosis of MDD was on average (SD) 13.7 (11.2) years prior to enrolling in the study. The current MDE had a mean (SD) duration of 2.6 (3.9) years and for 75.4% of the patients this was a recurrent episode.(29)

At baseline, 77.4% of the patients had moderate depression (MADRS 20–34) whereas the remainder 32.6% was classified as having severe depression (defined as MADRS >34). In addition, the percentage of patients who had failed on at least two ADs in the current episode was 99.5% of which 45.7% had failed on three or more and 14.6% had failed on four or more. The most prescribed AD prior to enrolment was SSRI (77.1%) and treatment failure on one SSRI during the current episode was reported for 76.2% of the patients at baseline. The second most commonly failed treatment was SNRIs of which 55.7% of the patients experienced failure to. Furthermore, a detailed overview of the main study characteristics of the TRD cohort study is available at table A2.8.(29)

Intervention

During the observation period, subjects will be treated both pharmacologically and non-pharmacologically in accordance with medical treatment practice, hereafter referred to as SOC. Non-interventional designs, such as this prospective cohort study, are characterised by the fact that all therapeutic measures are carried out in accordance with standard treatment practice and no specifications are made in this respect regarding the treatments.(29)

The study cohort was initiating a new treatment for depression at the start of the study (at the discretion of the treating physician and could be changed at any time during the study).(29)

In the context of the cohort, initiation of a new antidepressant treatment was any pharmacological and/or non-pharmacological (e.g., ElectroConvulsive Therapy [ECT], Transcranial Magnetic Stimulation [TMS], specific psychotherapy [i.e., cognitive behavioural therapy [CBT], interpersonal therapy [IPT]], etc.) treatment that was prescribed either to replace or was prescribed in addition to (i.e., on top of) the previously established antidepressant treatment with the intent to improve a patient's clinical depressive condition.(29)

The SOC treatments strategies at baseline were distributed as following (15):

- 35.4% of patients were on combination therapy (i.e. prescription of ≥2 antidepressant medications.)
- 36.7% of patients were treated with augmentation strategies (i.e. prescription of an add-on medication in addition to regular oral antidepressant)
- 23.2% of patients were on monotherapy (prescription of 1 antidepressant medication)

However, the use of monotherapy decreased as treatment strategies were changed, with 16.7% of the patients being on monotherapy in the third treatment since start of the study. Likewise, the use of combination therapy decreased with 30.6% of patients receiving a combination therapy as third treatment. In contrary, the percentage of patients on augmentation therapy increased as it accounted for 50.0% of patients completing a third treatment since starting the study.(15)

Study endpoints

The following patient-relevant endpoints were recorded in the TRD cohort (29, 30):

- Percentage of subjects with remission (MADRS total score ≤ 10 and MADRS total score ≤ 12)
- Percentage of subjects with response according to improvement in MADRS total score by at least 50% at baseline
- Change in depressive symptoms measured according to MADRS total score at month 6
- Change in the severity of the depressive disorder according to the CGI-S total score at month 7
- Change in general state of health according to mean EQ-5D-5L score at month 6
- Change in functional impairment according to SDS total score at month 6

Adverse events that occurred during the follow-up examination of subjects in the prospective TRD cohort study were reported via pharmacovigilance and not documented in the study itself.

Consequently, these outcomes can be used to evaluate what the effect of treatment with SoC is after 6 months, where it is determined whether stable clinical remission can be measured. Furthermore, as the treatments provided to the patients in the study was selected at the discretion of the treating physician and could be changed at any time during the study, combination therapy accounted for 41.4% of treatment strategies at baseline whereas monotherapy was used for 18.2% and 40.4% of strategies involved ≥1 augmentation drug

Analysis period

The TRD cohort was started on 05 March 2018 and ended on 31 March 2020

6 Clinical questions

6.1 What is the clinically added value of esketamine in combination with SSRI or SNRI compared to placebo in combination with SSRI or SNRI for the treatment of adults with treatment resistant depression, which have not responded on a least two different treatments with antidepressants in the current moderate to severe depressive episode.

6.1.1 Presentation of relevant studies

The clinical evidence for ESK-NS is derived from one phase 2a trial (SYNAPSE) and six Phase 3 trials: three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3), one maintenance study (SUSTAIN-1), and two long-term safety studies (SUSTAIN-2, SUSTAIN-3), see table 20.

- SYNAPSE was a dose response study of ESK-NS of 28 mg, 56 mg and 84 mg.(26)
- In TRANSFORM-1, with the exception of the first dose (56 mg), ESK-NS was administered at fixed doses of either 56 mg or 84 mg, which is not reflective of the approved licence.(19)
- The TRANSFORM-2 study evaluated the efficacy of flexible dosing (56mg/84mg) of ESK-NS, which is in line with its licence and use in clinical practice.(16)
- TRANSFORM-3 enrolled patients with TRD ≥65 years and for tolerability considerations, the starting dose of ESK-NS was 28 mg which was below the minimum effective dose (56 mg).(19)
- SUSTAIN-1 is a randomised, double-blind, long-term trial in adults (18–64 years) with TRD who had achieved stable remission or stable response comparing the maintenance of efficacy of continued flexible-dosed ESK-NS + OAD with OAD + PBO-NS.(17)
- SUSTAIN-2 was an open-label, multicenter, long-term study to evaluate the safety and efficacy of esketamine nasal spray plus a newly initiated oral AD in patients with TRD. Patients entered the study either directly (referred to as 'direct-entry patients') or after completing the double-blind induction phase of TRANSFORM-3.(33)
- SUSTAIN-3 was a phase III, multicenter, open-label, long-term extension study to evaluate the safety, tolerability, and efficacy or esketamine nasal spray in patients with TRD. Patients from all previously described phase III trials (TRANSFORM-1, -2 and -3, and SUSTAIN-1 and -2) will be eligible for enrolment.(25)

Furthermore, the TRD cohort study which was not part of the esketamine clinical development program are utilized in this submission dossier and results for clinical question 1 are presented in this section.

Table 20: Overview of clinical trials for ESK-NS (16-19, 25, 26, 33)

Trial	SYNAPSE	TRANSFORM-1	TRANSFORM-2	TRANSFORM-3	SUSTAIN-1	SUSTAIN-2	SUSTAIN-3
Study design	Phase IIa randomized, double-blind, placebo-controlled, multicenter study with 2 panels (Panel A in the US and Belgium, Panel B in Japan)	Randomised, double-blind, parallel-group, active-controlled, multicentre, Phase 3				Phase III, open-label, long-term, safety and efficacy study	Phase III, open-label, long-term, safety and efficacy study
Population	Adults (aged 20 to 64 years with single or recurrent TRD	Adults (aged 18–64 years) with recurrent or single-episode TRD		Adults (aged ≥65 years) with recurrent or single-episode TRD	Adults (aged 18–64 years) with recurrent or single-episode TRD.	Adults (aged 18 to 64 years and ≥ 65 years) with recurrent or single-episode TRD.	Population consisted of patients enrolled in TRANSFORM-1 to 3 and SUSTAIN-1 and SUSTAIN-2
Intervention(s)	1 to 6 sprays of ESK-NS 28 mg, 56 mg or 84 mg for up to 4 days (Days 1, 4, 8, 11) during the double-blind phase	Fixed dose ESK-NS (56 mg OR 84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 56 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (28 mg /56 mg/84 mg) twice weekly for 4 weeks (starting dose for all patients: 28 mg) + newly initiated OAD	Flexibly-dosed ESK-NS (56 mg/ 84 mg) weekly, or every other week in the maintenance phase until relapse or study termination plus + initiated OAD	Open-Label Induction Phase: ESK-NS twice per week for 4 weeks (56 mg or 84 mg for those < 65 years; 28 mg, 56 mg or 84 mg for those >= 65 years) hereafter in the optimization/ maintenance phase once weekly or once every. Transferred-entry responder participants from TRANSFORM-3, >= 65 years old will start at a dose of 28 mg in Week 5.	Induction phase: ESK-NS (56 mg or 84 mg twice a week for 4 weeks with 28 mg available for ≥ 65 years); optimization/ maintenance Phase: pt. entering post-induction (SUSTAIN-1, 2, 3), dose is the same and frequency is reduced to weekly for 4 weeks; for responders from TRANSFORM-3, dose will be initiated at 28 mg in week 1 then adjusted next 3 weeks.
Comparator(s)	1 to 6 sprays of placebo for 2 days (Days 1 and 4) or depending on response on Day 8, for 4 days (Days 1,4, 8, 11)	Newly initiated OAD + PBO-NS twice weekly for 4 weeks			Newly initiated OAD + PBO-NS twice weekly, or every other week until relapse or study termination	N/A	N/A

6.1.2 Results per study

6.1.3 TRANSFORM-1

Data from TRANSFORM-1 show that ESK-NS + a newly initiated OAD, provided clinically meaningful, rapid improvement of depressive symptoms in patients with TRD versus a newly initiated OAD + PBO-NS. The primary endpoint measured improvement in depressive symptoms, as assessed by the change in MADRS total score from baseline to Day 28 of induction (which numerically favoured the ESK-NS-56 mg + OAD and ESK-NS-84 mg + OAD arms over OAD + PBO-NS. (19)
Since the difference between the ESK-NS-84 mg + OAD and OAD + PBO-NS arms was not statistically significant (LS mean difference: –3.2; 1-sided p=0.044), in accordance with the predefined testing sequence, the ESK-NS-56 mg + OAD arm could not be formally evaluated. Similarly, the key secondary endpoints of onset of clinical response by Day 2 (maintained to Day 28) could not be formally evaluated. (19)
The results for TRANSFORM-1 are summarized in table A3a of section 8.2 in the appendix.

Serious adverse events

There were no deaths in the study however, two subjects experienced a serious adverse event (SAE) during the double-blind induction phase, see table 21. One subject in the ESK-NS 56 mg + OAD treatment group experienced an SAE of depression (reported term of "worsening of depression") on Day 15 of the double-blind induction phase. The investigator considered the event possibly related to ESK-NS+OAD. Another subject in the ESK-NS 56 mg + OAD treatment group experienced an SAE of headache (reported term of "headache") on Day 12 of the double-blind induction phase. The investigator considered the event probably related to ESK-NS and not related to OAD. (1, 19)
No patients in the OAD + PBO-NS group experienced SAEs during the double-blind induction phase. (1, 19)

Table 21: Overall incidence of serious adverse events in TRANSFORM-1 (1)

TRANSFORM-1 (Fixed-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	ESK-NS 56 mg:	115	2 (1.7%)	2
	ESK-NS 84 mg:	116	0 (0%)	0
	Total ESK-NS (56 mg and 84 mg)	231	2 (0.87%)	2
	PBO-NS:	113	0 (0%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

In total, 10 subjects experienced 1 or more treatment emergent adverse events (TEAEs) leading to discontinuation of intranasal study medication during the double-blind induction phase, see table 22.

Subjects who experienced a TEAE leading to discontinuation of intranasal study medication could have continued treatment with the OAD study medication in the follow-up phase if clinically appropriate.

- Among 115 subjects in the ESK-NS 56 mg + OAD treatment group, 1 (0.9%) subject discontinued ESK-NS on Study Day 15 of the double-blind induction phase due to a TEAE of depression (reported term of "worsening of depression"). (19)
- Among 116 subjects in the ESK-NS 84 mg + OAD treatment group, a total of 7 (6.0%) subjects discontinued ESK-NS due to TEAEs. The reported TEAEs were single events of anxiety, disturbance in attention, extrasystoles, headache, mania, motion sickness, panic attack, and tachycardia, and 2 events each of dizziness, nausea, and vomiting. (19)
- The majority of these subjects (5 of 7 subjects) discontinued after receiving only 1 intranasal dose of esketamine; per the study design, subjects in the ESK-NS 84 mg + OAD treatment group were to receive ESK-NS 56 mg on Day 1, followed by ESK-NS 84 mg on Day 4 and for all subsequent intranasal treatment sessions. Of the other 2 subjects, 1 subject discontinued ESK-NS due to TEAEs of nausea and vomiting on Day 14 (after receiving 4 intranasal doses), and the other subject discontinued due to a TEAE of panic attack on Day 5 (after receiving 2 intranasal doses). (19)
- Among 113 subjects in the PBO+OAD treatment group, 1 (0.9%) subject discontinued intranasal placebo due to a TEAE of insomnia, and 1 (0.9%) subject discontinued intranasal placebo due to a TEAE of erectile dysfunction. (19)

Table 22: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication in TRANSFORM-1 (19).

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
TRANSFORM-1	ESK-NS 56 mg + OAD	115	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	1	0.9
	ESK-NS 84 mg + OAD	116		7	6
	Total ESK-NS	231		8	3.5
	PBO-NS	113		2	1.8

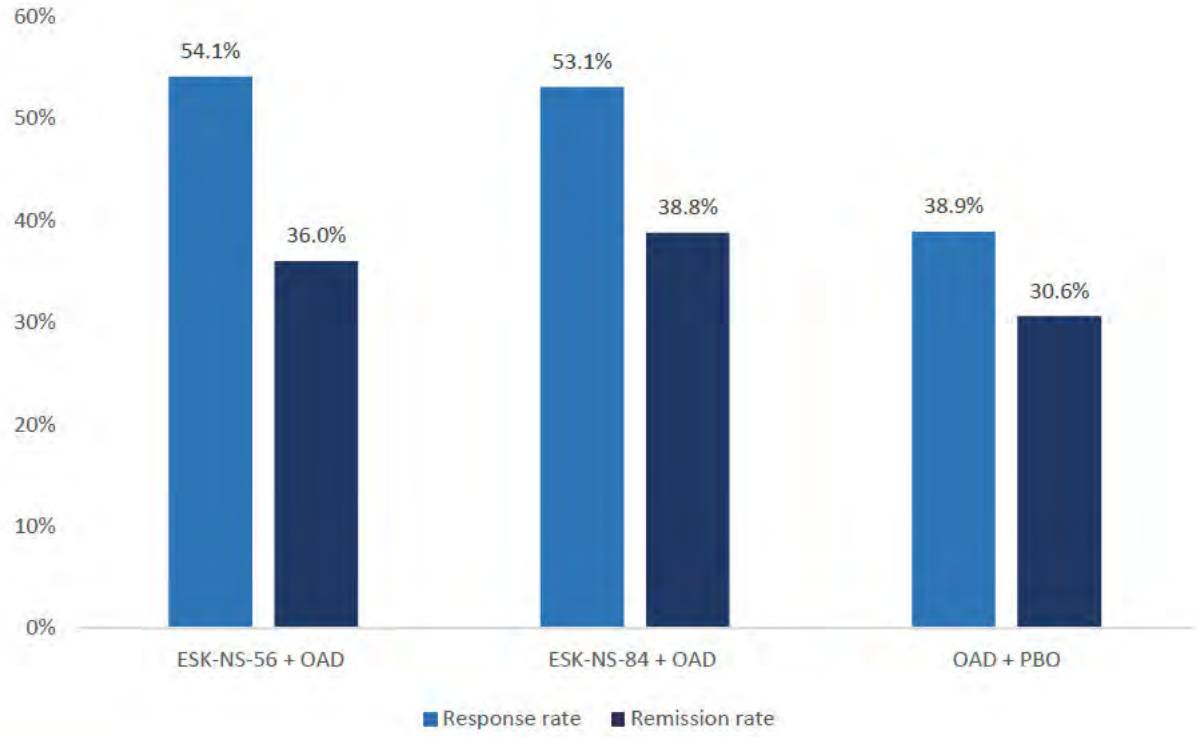
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Response rates based on MADRS total score (response defined as ≥50% reduction from baseline in MADRS total score) and remission rates based on MADRS total score (remission defined as MADRS total score ≤12) during the double-blind induction phase are presented in figure 10. The proportion of responders at Day 28 based on the MADRS total score (observed cases) were 60 of 111 subjects (54.1%), 52 of 98 subjects (53.1%), and 42 of 108 subjects (38.9%) for the ESK-NS 56 mg + OAD, the ESK-NS 84 mg + OAD, and the OAD + PBO-NS+ treatment groups, respectively. Furthermore, The proportion of subjects in remission at Day 28 were 40 of 111 subjects (36.0%), 38 of 98 subjects (38.8%), and 33 of 108 subjects (30.6%) for the ESK-NS 56 mg + OAD, the ESK-NS 84 mg + OAD, and OAD + PBO-NS treatment groups, respectively. (19)

Figure 10: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-1 (19).



Quality of life

Mean (SD) changes in Health Status Index (HSI) from baseline to the endpoint of the double-blind induction phase were 0.224 (0.2481) for subjects treated with ESK-NS 56 mg + OAD, 0.243 (0.2395) for subjects treated with ESK-NS 84 mg + OAD, and 0.181 (0.2495) for those treated with PBO-NS+OAD.(19)

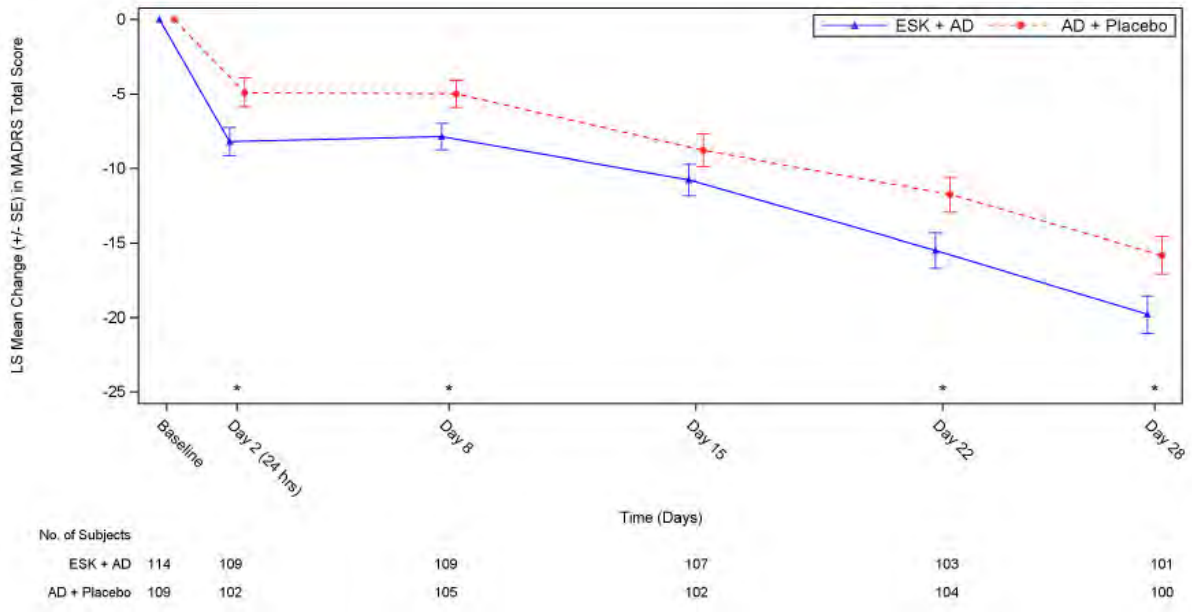
6.1.4 TRANSFORM-2

Data from TRANSFORM-2 show that ESK-NS + a newly initiated OAD, provided statistically significant, clinically meaningful, rapid improvement of depressive symptoms in patients with TRD versus a newly initiated OAD + PBO-NS. The results for TRANSFORM-2 are summarized in table A3b of section 8.2 in the appendix.

Additionally, ESK-NS has shown to act more quickly (as fast as 24 hours post-dose) compared with currently available antidepressant drugs. The TRANSFORM-2 study shows that ESK-NS + OAD induces about 20% higher response and remission levels at four weeks. TRANSFORM-2 met its primary endpoint, showing a statistically significant and clinically meaningful improvement in depressive symptoms, as assessed by MADRS, with ESK-NS + a newly initiated OAD versus a newly initiated OAD + PBO-NS. (16)

The mean (SD) change in MADRS total score from baseline to the end of the double-blind 4-week induction phase (Day 28) was –21.4 (12.32) in the ESK-NS + OAD arm and –17.0 (13.88) in the OAD + PBO-NS arm; LS mean (SE) difference was –4.0 (1.69; p=0.010), based on Mixed-effects model using repeated measures (MMRM), see figure 11. Most importantly, the superiority of ESK-NS + OAD compared with OAD + PBO-NS in change in MADRS total score at Week 4 translates into considerably higher remission and response rates. (16)

Figure 11: LS mean (SE) changes in MADRS total score over time (observed cases MMRM; full analysis set) (16)



Abbreviations: AD, antidepressant; ESK, esketamine; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model using repeated measures; SE, standard error.

Note: Change from baseline was the response variable and fixed effect model terms for treatment, day, country, class of OAD (SNRI or SSRI), treatment-by-day, and baseline MADRS value were covariates.

* 1-sided p<0.020.

Serious adverse events

One patient treated with ESK-NS + OAD experienced SAEs of road traffic accident and multiple injuries Day 16 of the double-blind induction phase, 1 day (approximately 28 hours) after receiving a dose of ESK-NS and study medication was withdrawn. This patient subsequently died on Day 55, 40 days after the last dose of ESK-NS. The investigator considered the events of road traffic accident and multiple injuries not related to

ESK-NS and not related to OAD. Furthermore, one patient in the OAD + PBO-NS group experienced an SAE in the double-blind induction phase (1, 16). See table 23 for an overview of SEAs.

Table 23: Overall incidence of serious adverse events in TRANSFORM-2 (1)

TRANSFORM-2 (Flexible-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	Esk-NS 56-84 mg:	115	1 (0.9%)	0
	PBO-NS:	109	1 (0.9%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

In total, 9 patients experienced 1 or more TEAEs leading to discontinuation of intranasal study medication: 8 (7.0%) of 115 patients in the ESK-NS + OAD group, and 1 (0.9%) of 109 patients in the OAD + PBO-NS group, see table 24. Patients in the ESK-NS + OAD group discontinued ESK-NS due to TEAEs of anxiety, depression, depressive symptom, panic attack, drug intolerance, feeling drunk, dizziness, headache, vertigo, nausea, multiple injuries and road traffic accident. One patients in the OAD + PBO-NS group discontinued intranasal placebo due to a TEAE of rash generalized. (16)

Table 24: Proportion of patients experiencing 1 or more TEAEs leading to discontinuation of intranasal study medication in TRANSFORM-2 (16).

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
TRANSFORM-2	ESK-NS + OAD	115	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	8	7
	OAD + PBO-NS	109		1	0.9

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

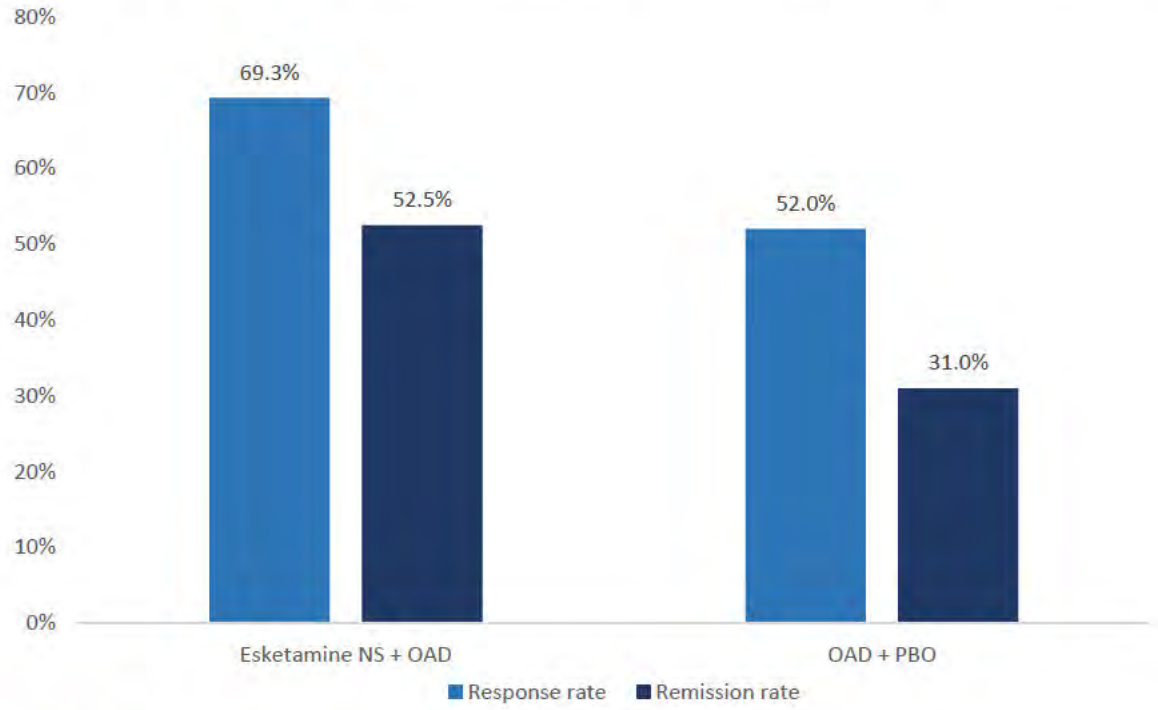
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Based on MADRS, higher response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates were achieved among patients treated with ESK-NS + OAD versus OAD + PBO-NS at week 4, see figure 12. Specifically, at Day 28, 70 (69.3%) of 101 subjects in the ESK-NS + OAD group and 52 (52.0%) of 100 subjects in the OAD + PBO-NS group were responders and 53 (52.5%) of 101 subjects in the ESK-NS + OAD group and 31 (31.0%) of 100 subjects in the OAD + PBO-NS group were in remission. (16) Furthermore a odds ratio of 2.4 (CI;1.30-4.54) was reported comparing the proportion of responders in the ESK-NS + OAD versus OAD + PBO-NS group at day 28. (16)
From a patient perspective, improved response and remission rates likely translate into greater improvements in mood, appetite, sleep, and concentration. Furthermore, these improved response and remission rates lead to a higher number of patients being able to care for themselves and their relatives as well as friends, go back to work, and live normal lives again.

Figure 12: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-2. (16)



Quality of life

ESK-NS + OAD treatment resulted in a greater improvement in health-related quality of life (HRQoL) versus OAD + PBO-NS, as shown by the increase from baseline in mean (SD) EQ-5D Health Status Index (HSI) score to Day 28 of induction. The Mean (SD) changes in HSI from baseline to the endpoint of the double-blind induction phase were 0.288 (0.2317) for subjects treated with ESK-NS+OAD and 0.231 (0.2506) for those treated with OAD+PBO-NS. Compared to OAD + PBO-NS, ESK-NS + OAD treatment resulted in more patients being able to care for themselves, who are more mobile, experience less pain and depression or anxiety, and a significant higher number of patients being able to resume their usual activities compared with OAD + PBO-NS. (1)

6.1.5 TRANSFORM-3

Data from TRANSFORM-3 show that ESK-NS + a newly initiated OAD, provided clinically meaningful, rapid improvement of depressive symptoms in elderly patients with TRD versus a newly initiated OAD + PBO-NS. The results for TRANSFORM-3 are summarized in table A3c of section 8.2 in the appendix.
Though not statistically significant, improvement in depressive symptoms, as assessed by the change in MADRS total score from baseline to Day 28 of induction (MMRM), numerically favoured ESK-NS + OAD over OAD + PBO-NS for the treatment of adult patients aged ≥65 years with TRD.
Improvement in depressive symptoms, as assessed by the mean (SD) change in MADRS total score from baseline in the ESK-NS + OAD arm was –10.0 (12.74) versus –6.3 (8.86) in the OAD + PBO-NS arm (LS mean difference: –3.6; two-sided p = 0.059) (18)

Serious adverse events

There were no deaths in the study however five subjects reported a serious TEAE during the double-blind induction phase, see table 25.
In the ESK-NS + OAD group, one subject reported a serious TEAE of anxiety disorder. The investigator considered the event possibly related to ESK-NS and possibly related to OAD. Furthermore, one subject in the ESK-NS + OAD group reported a serious TEAE of blood pressure (BP) increased which the investigator considered the event probably related to ESK-NS and not related to OAD. The last patient in the ESK-NS + OAD group reported a hip fracture. The investigator considered the event not related to ESK-NS and not related to OAD. (18)

For the OAD + PBO-NS group one subject reported serious TEAEs of gait disturbance which the investigator considered be possibly related to PBO-NS and very likely related to OAD. Furthermore, one subject in the OAD + PBO-NS group reported a serious TEAE of dizziness. The investigator considered the event to be doubtfully related to PBO-NS and doubtfully related to OAD. (18)

Table 25: Overall incidence of serious adverse events in TRANSFORM-3 (1)

TRANSFORM-3 (Flexible-Dose)	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction Phase	Esk-NS 28-84 mg:	72	3 (4.2%)	2
	PBO-NS:	65	2 (3.1%)	1

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

Four of 72 (5.6%) subjects in the ESK-NS + OAD group, and 2 of 65 (3.1%) subjects in the OAD + PBO-NS group experienced 1 or more TEAEs leading to discontinuation of intranasal study medication, see table 26. Subjects in the ESK-NS + OAD group discontinued ESK-NS due to TEAEs of anxiety disorder, BP increased, BP systolic increased, and hip fracture. (18)

Table 26: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication in TRANSFORM-3. (18)

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
TRANSFORM-2	ESK-NS + OAD	72	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	4	5.6
	OAD + PBO-NS	65		2	3.1

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

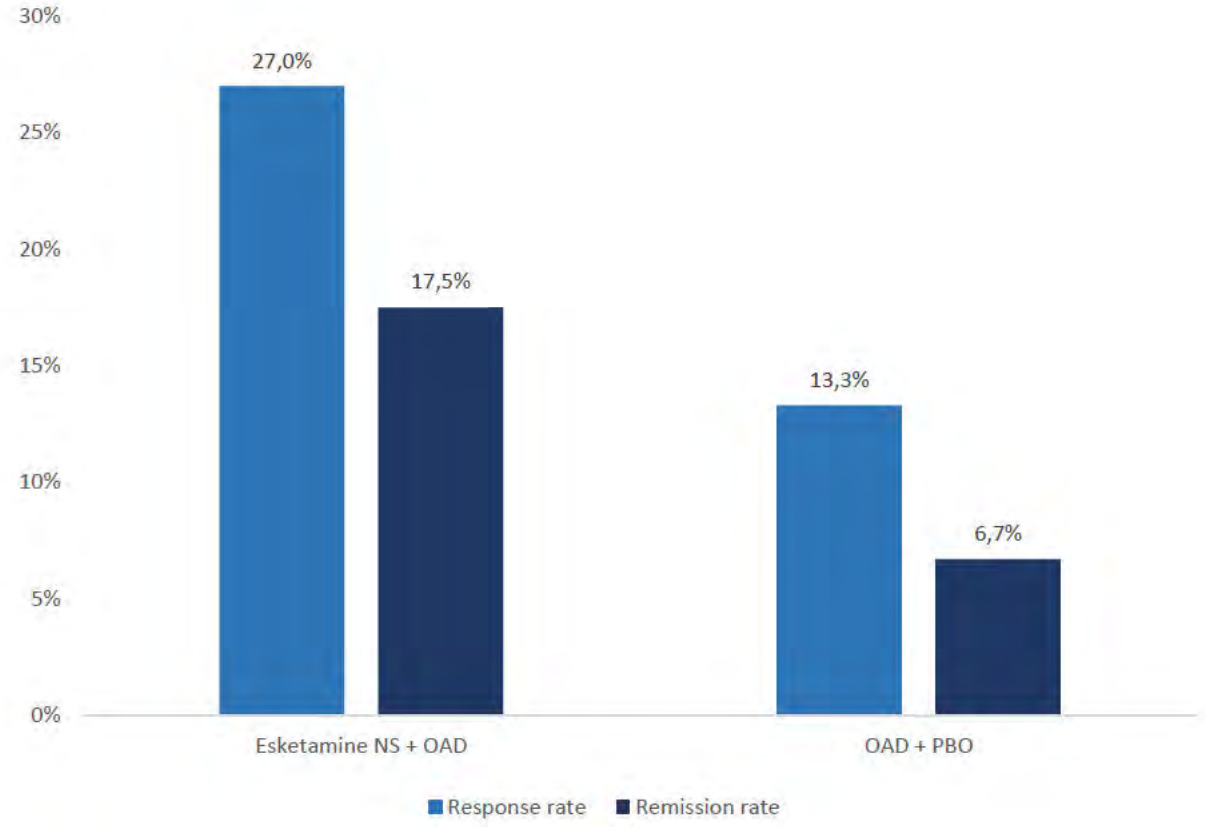
Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Response rates based on MADRS total score (response defined as ≥50% reduction from baseline in MADRS total score) and remission (MADRS total score of ≤12) rates during the double-blind induction phase are presented in figure 13. The proportion of responders in both treatment groups generally increased over time during the double-blind induction phase. Overall response rates at Day 28 numerically favored the ESK-NS + OAD group (17 of 63 [27.0%] subjects) compared with OAD + PBO-NS (8 of 60 [13.3%] subjects). At Day 28, 11 of 63 (17.5%) subjects in the ESK-NS + OAD group and 4 of 60 (6.7%) subjects in the OAD + PBO-NS group were in remission. (18)

Figure 13: Day 28 response and remission rates based on MADRS (observed cases) in TRANSFORM-3. (18)



Quality of life

Mean (SD) changes in HSI from baseline to the endpoint of the double-blind induction phase were 0.081 (0.2624) for subjects treated with ESK-NS + OAD and 0.026 (0.2235) for those treated with OAD + PBO-NS. (40).

6.1.6 SUSTAIN-1

In SUSTAIN-1, maintenance treatment with ESK-NS + OAD significantly reduced relapse rates in patients with TRD aged 18–64 years. Relapse rates were lower both in patients in stable remission and those in stable response who, at randomisation, continued ESK-NS + OAD compared with those who, at randomisation, continued the same OAD but switched to PBO-NS from ESK-NS.
After 16 weeks of initial treatment with ESK-NS, ongoing ESK-NS + OAD treatment also significantly delayed worsening of symptom severity and functional impairment during the maintenance phase compared with OAD + PBO-NS, based on mean changes over time in MADRS (in both stable remitter and responder patients). In a consistent manner, continuing ESK-NS + OAD treatment was associated with smaller deterioration in HRQoL (EQ-5D-5L HSI) over the duration of the maintenance phase, compared with those who continued their OAD but switched to PBO-NS. (17)
Overall, the SUSTAIN-1 data show that after 16 weeks of initial ESK-NS treatment, maintenance treatment with ESK-NS + OAD is associated with sustained improvement in patient social and occupational functioning and quality of life, which will have a positive impact on not only the patients themselves, but also their family, friends and carers. (17)
The results for SUSTAIN-1 are summarized in table A3d of section 8.2 in the appendix.

Serious adverse events

SAEs were reported in the ESK-NS + OAD group by 13 of 437 (3.0%) subjects during the open-label induction phase, 11 of 455 (2.4%) subjects during the optimization phase, and 4 of 152 (2.6%) subjects during the maintenance phase, see table 27. In the OAD + PBO-NS group, SAEs were reported during the maintenance phase by one subject (0.7%) in the safety (MA) analysis set. (1) SAEs considered by the investigator as related to study drug were reported for 6 patients in the ESK-NS + OAD group (autonomic nervous system imbalance, disorientation, hypothermia, lacunar stroke [ie, ischemic lesion, day 1, 6 hours after dosing], sedation, simple partial seizures [day 5, 45 minutes after dosing; no seizure history], and suicidal ideation) during the induction phase. (17)

Table 27: Overall incidence of SAEs in SUSTAIN-1. (1)

SUSTAIN-1	Treatment (+ Oral AD)	N	SAE	SAE Considered as at Least Possibly Related
Induction phase	Esk-NS 56-84 mg:	437	13 (3.0%)	6 (1.4%)
Optimization phase	Esk-NS 56-84 mg:	455	11 (2.4%)	0
Maintenance Phase	Esk-NS 56-84 mg:	152	4 (2.6%)	0
	PBO-NS:	145	1 (0.7%)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

Seven patients experienced 1 or more AEs during the maintenance phase, leading to discontinuation of the intranasal study drug, see table 28; 4 (2.6%) of 152 were in the ESK-NS + OAD group (worsening depression, 3 patients; anxiety and confusional state [transient], 1 patient) and 3 (2.1%) of 145 were in the OAD + PBO-NS (worsening depression for each). (17)

Table 28: Proportion of patients experiencing 1 or more TEATs leading to discontinuation of intranasal study medication during the maintenance phase of SUSTAIN-1.

Trial	Randomised interventions	N	Definition of discontinuation	Incidence of discontinuation	
				n	%
SUSTAIN-1	ESK-NS + OAD	152	Patients experiencing ≥1 TEAE leading to discontinuation of intranasal study medication	4	2.6
	OAD + PBO-NS	145		3	2.1

Abbreviations; SNRI, serotonin–norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Based on MADRS definitions, the proportions of patients in stable remission and stable response, who had maintained their remitter/responder status by the end of the maintenance phase, were consistently higher among ESK-NS + OAD patients than OAD + PBO-NS, see table 29. (40) Overall, the results of SUSTAIN-1 indicate sustained improvements in the physician-reported symptoms of depression (mood, tension, sleep, appetite, concentration, lassitude, and empathy) as well as in patient-reported depressive symptoms and functional impairment/disability. Additional analyses using a different methodology than LOCF are available in appendix 8.6. This is delivered based on a request by the Medicines Council.

Table 29: Response and remission rates over the duration of the maintenance (MA) phase based on MADRS.(41)

	Full (stable remitters) analysis set N=176		Full (stable responders) analysis set N=121	
	ESK-NS + OAD N=90	OAD + PBO-NS N=86	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Response/remission based on MADRS, n/N (%)				
Responder at beginning of MA	90/90 (100.0)	86/86 (100.0)	62/62 (100.0)	59/59 (100.0)
Responder at end of MA	67/89 (75.3)	48/86 (55.8)	41/62 (66.1)	20/59 (33.9)
Remitter at beginning of MA	90/90 (100.0)	85/86 (98.8)[a]	37/62 (59.7)	38/59 (64.4)
Remitter at end of MA	58/89 (65.2)	36/86 (41.9)	29/62 (46.8)	15/59 (25.4)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; LOCF, last observation carried forward; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] one patient was incorrectly randomised.

Overall, among the patients who achieved stable response, 16 patients (25.8%) in the ESK-NS + OAD group and 34 patients (57.6%) in the OAD + PBO-NS group experienced relapse; among patients who achieved stable remission, 24 patients (26.7%) in the ESK-NS + OAD and 39 patients (45.3%) in the OAD + PBO-NS group experienced a relapse event during the maintenance phase, see table 30 and 31 respectively. Continued treatment with ESK-NS + OAD significantly delayed relapse compared with treatment with OAD + PBO-NS. Patients who achieved stable response, see figure 14: Hazard ratio 0.30; 95% CI, 0.16-0.55: $P <$ .001, NNT, 4). Patients who achieved stable remission, figure 15: HR, (HR), 0.49; 95% CI, 0.29-0.84; $P = .003$, number needed to treat [NNT], 6).(17)

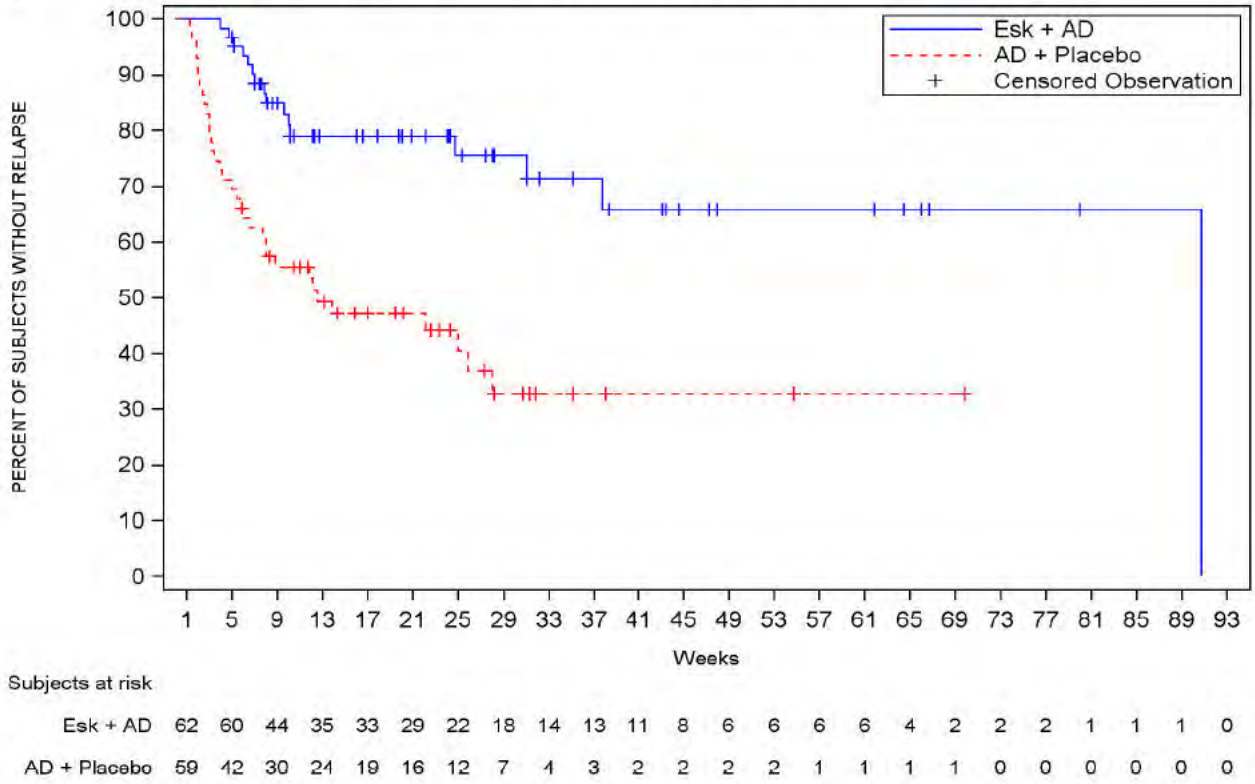
Table 30: Time to relapse and proportions of patients remaining relapse-free/stable responders (17)

	ESK-NS + OAD N=62	OAD + PBO-NS N=59
Time to relapse (days)[a]		
Patients assessed, n (%)	62 (100.0)	59 (100.0)
Patients censored, n (%)	46 (74.2)	25 (42.4)
Relapses, n (%)	16 (25.8)	34 (57.6)
25th percentile (95% CI)	217.0 (56.0; 635.0)	24.0 (17.0; 46.0)
Median (95% CI)	635.0 (264.0; 635.0)	88.0 (46.0; 196.0)
75th percentile (95% CI)	635.0 (NE)	NE
HR (95% CI)[b]	0.30 (0.16; 0.55)	
2-sided p-value[c]	<0.001	

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.

[b] Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor.
[c] Log-rank test.

Figure 14: Cumulative proportion of patient who remained relapse-free/stable responders (17)



Abbreviations: AD, antidepressant; Esk, esketamine.

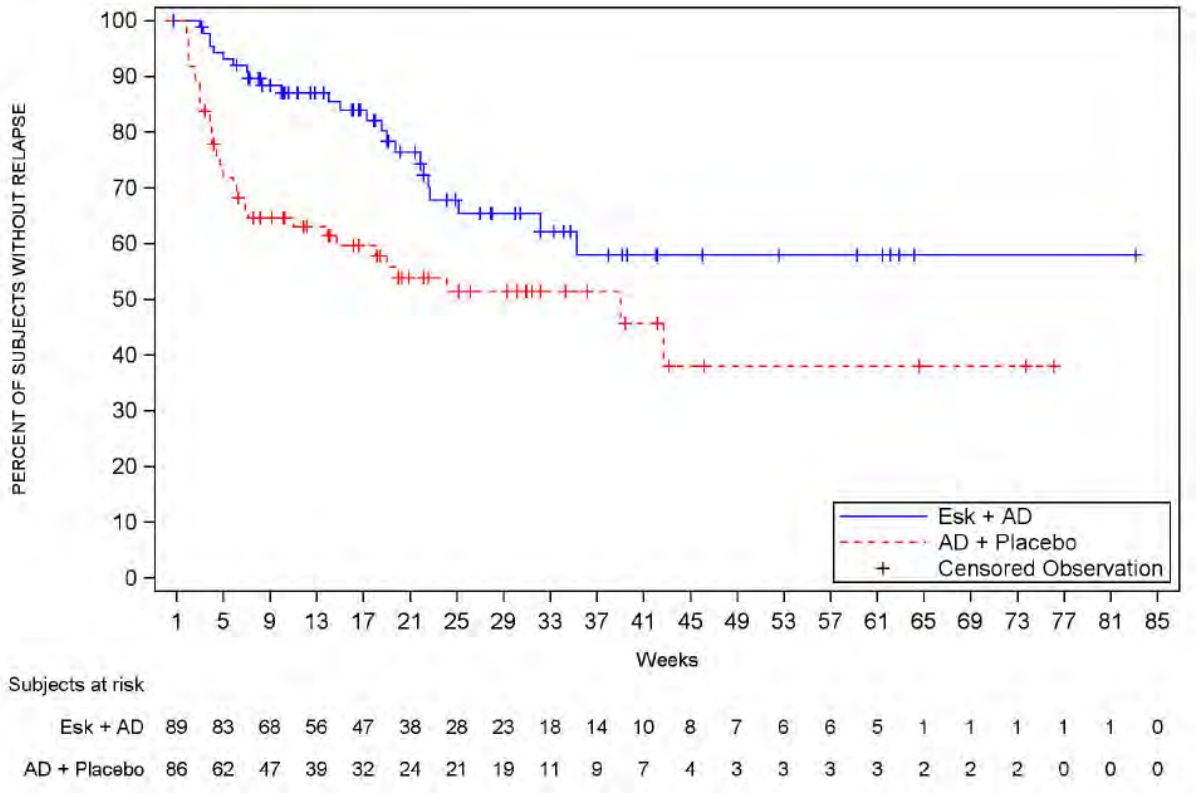
Table 31. Time to relapse and proportions of patients remaining relapse-free/stable remitters (17)

	ESK-NS + OAD N=90	OAD + PBO-NS N=86
Time to relapse (days)[a]		
Patients assessed, n (%)	90	86
Patients censored, n (%)	66 (73.3)	47 (54.7)
Relapses, n (%)	24 (26.7)	39 (45.3)
25th percentile (95% CI)	153.0 (105.0; 225.0)	33.0 (22.0; 48.0)
Median (95% CI)	NE	273.0 (97.0; NE)
75th percentile (95% CI)	NE	NE
HR (95% CI)[b]	0.49 (0.29; 0.84)	-
2-sided p-value[c]	0.003	-

Abbreviations: CI, confidence interval; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HR, hazard ratio; NE, not estimable; OAD + PBO-NS, newly initiated oral antidepressant plus placebo nasal spray.
[a] Based on Kaplan-Meier product limit estimates.

[b] HRs and CIs are weighted estimates based on Wassmer (2006) (42) and calculated using R.
[c] Based on the final test statistic which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters.

Figure 15: Cumulative proportion of patient who remained relapse-free/stable remitters (17)



Abbreviations: AD, oral antidepressant; Esk, esketamine nasal spray.

Quality of life

In both stable remitters and stable responders, those in the ESK-NS + OAD arm experienced smaller reductions in HRQoL (EQ-5D-5L HSI) compared with those in the OAD + PBO-NS arm over the duration of the maintenance phase. Mean (SD) changes in HSI from baseline of the maintenance phase to the endpoint of the maintenance phase among stable remitters were -0.067 (0.1180) for subjects treated with ESK-NS + OAD and -0.096 (0.1484) for those treated with OAD + PBO-NS. (40) In addition the mean (SD) changes in HSI for stable responders were -0.023 (0.0753) for subjects treated with ESK-NS + OAD and -0.073 (0.1383) for those treated with OAD + PBO-NS. (40)

These results show that ESK-NS + OAD treatment maintained the increase in quality of life more sufficiently over the cause of the maintenance phase compared to OAD + PBO-NS. Consequently, more patients will remain being able to care for themselves, being more mobile, experience less pain and depression or anxiety, and a higher number of patients will remain being able to resume their usual activities compared with OAD + PBO-NS.

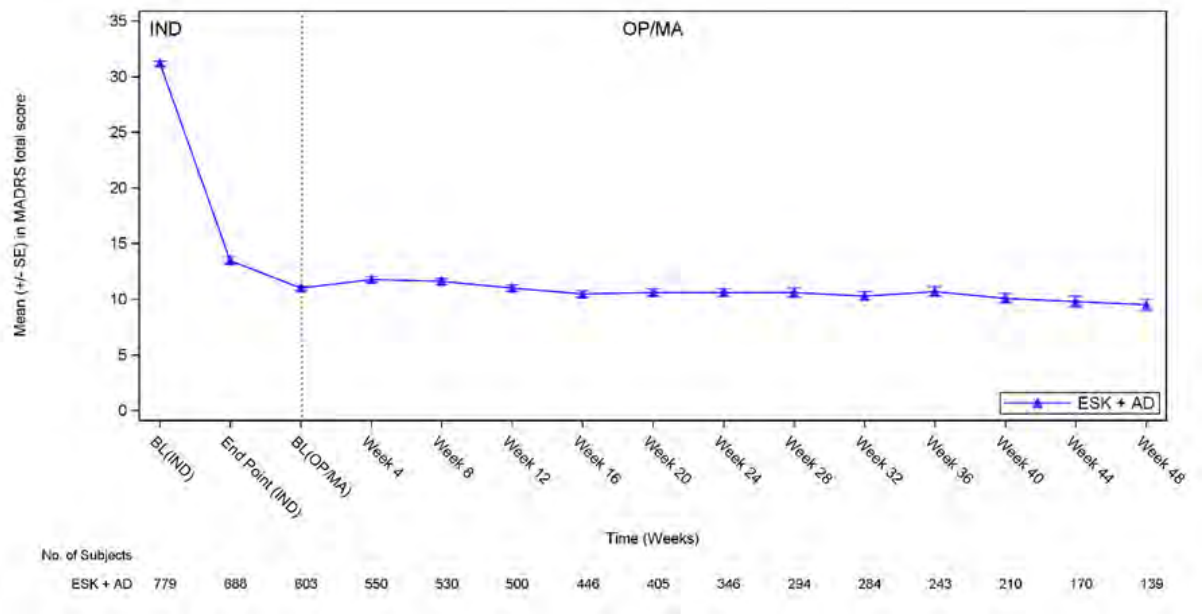
6.1.7 SUSTAIN-2

Results for SUSTAIN-2 are presented as reported in the published study by Wajs et al. 2020 and on ClinicalTrials.gov.(33) However, additional post-hoc analyses on MADRS total score change from baseline response and remission results at 6 months are presented as they constitute the basis of an indirect treatment comparison between the SUSTAIN-2 study and the TRD cohort study. The results for SUSTAIN-2 are summarized in table A3e of section 8.2 in the appendix and the analysis method for estimating results at 6 months as well as method of the indirect treatment comparison is available in section 8.5.1 in the appendix.

MADRS total score at optimization/maintenance

SUSTAIN-2 showed that the mean MADRS total score decreased in the induction phase with a mean change from induction baseline to endpoint of -16.4 (SD; 8,76). Furthermore, results from SUSTAIN-2 showed that ESK-NS + OAD demonstrated sustained remission of TRD, see figure 16. From the end of the induction phase to the endpoint of the optimization/maintenance phase, the mean change in MADRS total score was 0.3 (SD; 8,12) for esketamine nasal spray plus oral AD.(33)

Figure 16: Arithmetic Means (+/- SE) for MADRS Total Score over Time Observed Case (SUSTAIN-2: All Enrolled Analysis Set)(33)



Abbreviations: IND, induction; BL, baseline; OP/MA, optimization/maintenance
No of subjects, is the number of subjects who had a MADRS assessment at a given timepoint of the OP/MA phase

MADRS total score at 6 months

In addition to the results described above, the post-hoc analyses showed that the mean MADRS total score decreased from baseline to endpoint at 6 months with a mean change of [redacted] see table 32.

Table 32: Summary of SUSTAIN-2 post-hoc analyses on change in depressive symptoms according to MADRS total score from baseline to 6 months.(40)

[redacted]

Serious adverse events

SAEs were reported in 55 of 802 (6.9%) patient during the induction and optimization/maintenance phases for the all enrolled analysis set. Four patients had in total five SAE assessed as related (possibly, probably or very likely) to esketamine nasal spray by the investigators: delirium (n=1) , anxiety and delusion (both in 1 patient), suicidal ideation (n=1) and suicidal attempt (n=1).(33) For an overview of SAEs occurring in the different phases of the study, see table 33 and paragraphs hereafter.

In addition, 2.2% (17 of 779 subjects) reported SAEs during the induction phase and 6.3% (38 of 603 subjects) reported SAEs during the optimization/maintenance phase. Serious adverse events were reported during the follow-up phase in 2.2% (8 of 357) of subjects. An additional SAE was reported for a subject after leaving the study. The most common SAEs (in ≥2 subjects) were depression (1.0%; 8 subjects), suicidal ideation (0.7%; 6 subjects), suicide attempt (0.7%; 6 subjects), anxiety (0.2%; 2 subjects), and gastroenteritis (0.2%; 2 subjects). Most SAEs were in the psychiatric disorders SOC (3.2%; 26 subjects). During treatment, more than half of subjects with SAEs (32 of 55 subjects) reported at least one SAE that was considered severe in intensity. The SAEs of most subjects recovered or were recovering and were assessed by the investigator to be not related or doubtfully related to esketamine treatment. (33, 34)

Table 33: Overall summary of SAEs in induction and optimization/maintenance phases in SUSTAIN-2 (33, 34)

SUSTAIN-2	Treatment	N	SAE	SAE Considered as at Least Possibly Related
All enrolled analysis set	ESK-NS + OAD	802	55 (6.9%)	4 (0.5%)
Induction phase	ESK-NS + OAD	779	17 (2.2%)	n/a
Optimization/maintenance phase	ESK-NS + OAD	603	38 (6.3%)	n/A

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: Serious AEs with onset during the follow-up phase are not included.

Discontinuation due to adverse events

Overall, there were 9.5% of subjects (76 of 802 subjects) who discontinued esketamine treatment due to an adverse event during either treatment phase, see table 34. Most of the adverse events leading to discontinuation were in the psychiatric (4.0%) or nervous system disorders (1.6%) SOCs. The most common adverse events (≥5 subjects) leading to discontinuation of esketamine treatment were anxiety (1.1%; 9 subjects), suicidal ideation (0.9%; 7), depression (0.7%; 6), dizziness (0.7%; 6), blood pressure increased (0.7%; 6), and dissociation (0.6%; 5). Of the subjects with most common adverse events that led to discontinuation, 56.8% (21 of 37) discontinued during the induction phase within 2 weeks of the start of treatment.(33)
The percentage of subjects with events leading to discontinuation of esketamine treatment in each of the treatment phases was 6.8% (53 of 779 subjects) and 3.8% (23 of 603 subjects) in the induction and optimization/maintenance phase, respectively.(33)

Table 34: Proportion of patients experiencing 1 or more TEAEs leading to discontinuation of intranasal study medication in SUSTAIN-2 (all enrolled analysis set)(33)

Adverse event	IND phase (n=779), n (%)	OP/MA phase (n=603), n (%)	IND and OP/MA phase (N=802), n (%)
Most common TEAEs (≥ 2 patients) leading to discontinuation of esketamine nasal spray			
Anxiety	9 (1.2)	0	9 (1.1)
Suicidal ideation	3 (0.4)	4 (0.7)	7 (0.9)
Depression	3 (0.4)	3 (0.5)	6 (0.7)
Dizziness	6 (0.8)	0	6 (0.7)
Blood pressure increased	4 (0.5)	2 (0.3)	6 (0.7)
Dissociation	5 (0.6)	0	5 (0.6)
Muscular weakness	4 (0.5)	0	4 (0.5)
Vomiting	3 (0.4)	0	3 (0.4)
Hypertension	2 (0.3)	1 (0.2)	3 (0.4)
Suicide attempt	1 (0.1)	1 (0.2)	2 (0.2)
Headache	2 (0.3)	0	2 (0.2)
Sedation	2 (0.3)	0	2 (0.2)
Somnolence	2 (0.3)	0	2 (0.2)
Nausea	2 (0.3)	0	2 (0.2)
Vertigo	1 (0.1)	1 (0.2)	2 (0.2)

[a]A TEAE that started in one phase and resulted in discontinuation in the following phase is counted as TEAE in the phase of which the onset occurred.

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response at optimization/maintenance

The proportion of patients with response based on the MADRS total score (response defined as ≥50% reduction, ie, improvement from baseline of the induction phase), was 78.4% (593 of 756) at endpoint of

the induction phase, see table 35. Furthermore, during the optimization/maintenance phase, the percentage of responders was 76.5% (461 of 603) at endpoint of the optimization/maintenance phase.(33)

In addition the proportion of patients with remission based on the MADRS total score (remission defined as MADRS total score ≤12), was 47.2% (357 of 756) at endpoint of the induction phase, see table 35. Furthermore, during the optimization/maintenance phase, 58.2% (351 of 603) of subjects were in remission at endpoint of the optimization/maintenance phase.(33) Additional analyses using a different methodology than LOCF are available in appendix 8.7. This is delivered based on a request by the Medicines Council.

Table 35: Summary of SUSTAIN-2 Response and remission results (LOCF; full [IND] and full [OP/MA] analysis sets)(33)

Endpoint	ESK-NS + OAD N=779
MADRS	
Responder (based on MADRS) at end of induction, n/N (%)	593/756 (78.4)
Responder (based on MADRS) at end of OP/MA, n/N (%)	461/603 (76.5)
Remitter (based on MADRS) at end of induction, n/N (%)	357/756 (47.2)
Remitter (based on MADRS) at end of OP/MA, n/N (%)	351/603 (58.2)

Abbreviations: ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; IND, induction; LOCF, last observation carried forward; MA, maintenance phase; MADRS, Montgomery-Asberg Depression Rating Scale; OP, optimisation phase; SD, standard deviation.

Remission and Response at 6 months

The post-hoc analyses on response at 6 months showed that the proportion of patients with response based on the MADRS total score (response defined as ≥50% reduction, ie, improvement from baseline of the induction phase), was [redacted]). In addition, the proportion of patients with remission based on the MADRS total score (remission defined as MADRS total score ≤ 10), was [redacted] at 6 months, see table 36.

Table 36: Summary of SUSTAIN-2 post-hoc analyses on response and remission results at 6 months

[redacted]

Quality of life

ESK-NS + OAD treatment resulted in an improvement in health-related quality of life, as shown by the increase from baseline in mean (SD) EQ-5D-5L Health Status Index (HSI) score to end of induction, see table 37. The Mean (SD) changes in HSI from baseline to the end of the induction phase was were 0.190 (0.2138) for subjects treated with ESK-NS+OAD. From baseline of the optimization/maintenance phase the mean (SD) changes in EQ-5D-5L HIS score was -0.009 (0.1411) Consequently, quality of life improved from baseline (induction) to the endpoint of the induction phase. These improvements appeared to be maintained from baseline (optimization/maintenance) to the endpoint of the optimization/maintenance phase.(34)

Table 37: Summary of SUSTAIN-2 EQ-ED-5L results (LOCF; full [IND] and full [OP/MA] analysis sets)(34)

Endpoint	ESK-NS + OAD N=779
EQ-5D-5L	
Mean (SD) change in HSI from baseline to end of induction	0.190 (0.2138) (n=745)
Mean (SD) change in HSI from baseline (OP/MA) to end of OP/MA	–0.009 (0.1411) (n=603)

Abbreviations: EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESK-NS + OAD, esketamine nasal spray (flexibly-dosed) plus a newly initiated oral antidepressant; HSI, health status index; IND, induction; LOCF, last observation carried forward; MA, maintenance phase; OP, optimisation phase; SD, standard deviation.

6.1.8 SUSTAIN-3

Results for SUSTAIN-3 are presented as reported in an unpublished interim abbreviated clinical study report with data cutoff date being the 20th of May 2020. Thus, the results presented are confidential. The results for SUSTAIN-3 are summarized in table A3f of section 8.2 in the appendix.

Serious adverse events

Serious AEs reported in the SUSTAIN-3 study are detailed for the full period i.e. (induction plus optimization/maintenance phases) as well as separately for the induction phase and optimization/maintenance phase. Furthermore, SAEs during the different phases by age group is also described in the following.

Induction plus optimization/maintenance phases

[redacted]

Optimization/Maintenance Phase

[redacted]

[redacted]

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission and Response

Efficacy data on remission and response is not reported in the open-label long-term extension safety study of esketamine nasal spray in treatment resistant depression (SUSTAIN-3).(24)

Quality of life

Efficacy data on EQ-5D-5L HSI is not reported in the open-label long-term extension safety study of esketamine nasal spray in treatment resistant depression (SUSTAIN-3).(24)

6.1.9 SYNAPSE

SYNAPSE investigated esketamine nasal spray (without OAD combination) for the treatment of patients with moderate to severe MDD who failed to respond to at least 2 AD therapies during their current MDD episode (History of inadequate response to ≥2 ADs of which ≥1 AD was used in the current episode of depression). It should be noted that this inclusion criteria differs from the TRD definition as well as the populations studied in the Phase III trials.(26) Consequently, this should be kept in mind when assessing the result reported for SYNAPSE. The results for SYNAPSE are summarized in table A3g of section 8.2 in the appendix.

MADRS total score

Change in MADRS Total Score from Baseline to Day 8

Pairwise comparisons based on the analysis of the primary efficacy end point, the change in MADRS total score from Study Day 1 (Period 1 baseline) to Study Day 8 in Period 1 and change from Study Day 8 (Period 2 baseline) to Study Day 15 in Period 2, with the analysis based on data combined across both periods of the double blind phase, an efficacy signal was detected for each esketamine dose group versus placebo based on the weighted combination test at the one-sided 0.05 significance level. These mean differences represent the difference from placebo on Day 8 (after one week of treatment) and were estimated using data from both Period 1 and Period 2.(26)

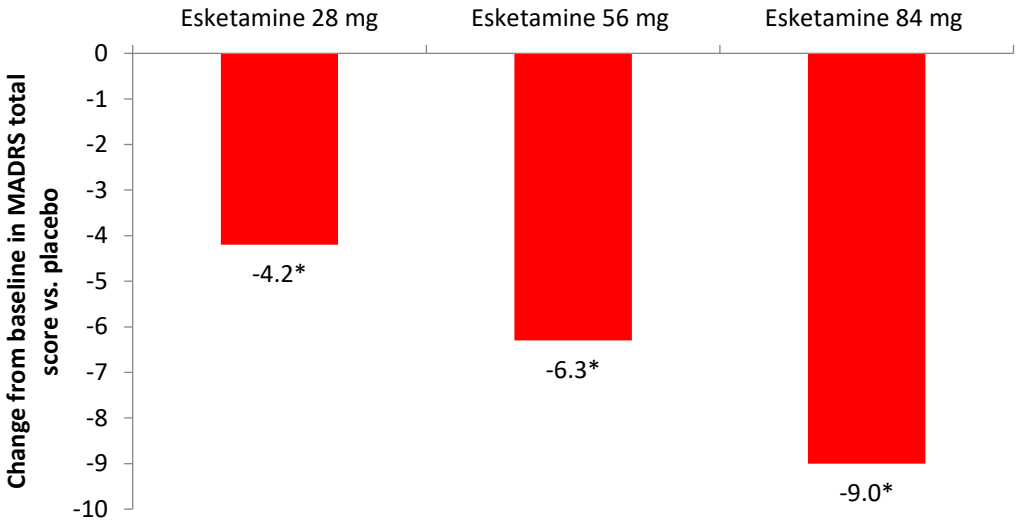
At the end of Period 1, MADRS total scores improved (decreased from Study Day 1 to Study Day 8) in all treatment groups in Panel A. Greater improvements were observed in the esketamine groups compared with the placebo group; the least squares mean treatment differences (SE) between each esketamine dose group and the placebo group were: -5.0 (2.99) for esketamine 28 mg, -7.6 (2.91) for esketamine 56 mg, and -10.5 (2.79) for esketamine 84 mg. In Period 2, greater improvements in MADRS total score from Study Day 8 to Study Day 15 were also observed in the esketamine groups compared with the placebo group; the least squares mean treatment differences (SE) between each esketamine dose group and the placebo group were: -3.1 (2.99) for esketamine 28 mg, -4.4 (3.06) for esketamine 56 mg, and -6.9 (3.41) for esketamine 84 mg.(26)

Change in MADRS Total Score from Baseline to Day 15

The decreases in MADRS total score were greater in the esketamine treatment groups compared with the placebo group at the double-blind endpoint (Study Day 15). Within the esketamine treatment group, the greatest decrease in MADRS total score was seen with the 84-mg dose, followed by the 56-mg dose, whereas the 28-mg dose had the least decrease and appeared less able to sustain the improvement over the 2 weeks duration, suggesting it would need to be given at a higher frequency than twice a week to sustain AD response. From day one to day 15, the mean difference in MADRS change versus placebo nasal spray for the esketamine nasal spray 28 mg, esketamine nasal spray 56 mg and esketamine nasal spray 84 mg was -4.2, -6.3, -9.0, respectively, see figure 17. Changes in MADRS score were observed within two hours of esketamine nasal spray administration.(26)

As placebo non-responders were randomly reassigned to treatment after Period 1 and may have received active treatment in Period 2, the estimate for patients who received placebo for both periods needed to be adjusted. The unadjusted estimate for the placebo/placebo group was overly optimistic because placebo patients who did not respond to treatment in Period 1 (patients with QIDS-SR16 total score ≥11) and were reassigned to esketamine treatment in Period 2 were not included in the computation of the estimate. The adjusted treatment differences were: -6.0 for esketamine 28 mg, -8.3 for esketamine 56 mg, and -12.5 for esketamine 84 mg.(26)

Figure 17: Estimated Mean Differences in MADRS Total Score between Esketamine and Placebo Groups (Period 1 and 2) after 1 week of treatment.(26)



*statistically significant versus placebo at the 0.05 significance level

Abbreviations: MADRS: Montgomery–Åsberg Depression Rating Scale

Serious adverse events

No ESK-NS patients or PBO patients in Panel A during the double-blind phase experienced a serious adverse events, see table 38.(27)

Table 38: Serious adverse events reported during the double-blind phase in SYNAPSE

Serious adverse events	PBO (Panel A and B: Period 1)[a]	ESK-NS 28 mg (Panel A: Period 1)	ESK-NS 28 mg (Panel A: Period 2)	ESK-NS 56 mg (Panel A and B: Period 1)[b]	ESK-NS 56 mg (Panel A and B: Period 2)[b]	ESK-NS 84 mg (Panel A: Period 1)	ESK-NS 84 mg (Panel A: Period 2)
Total (n/N) (%)	0/54 (0.00 %)	0/11 (0.0 0%)	0/16 (0.00 %)	0/20 (0.00 %)	0/32 (0.00 %)	0/12 (0.00 %)	0/17 (0.00 %)

A: Data reported for both panel A and panel B for PBO as stratified data on panel A and panel B is not reported at clinicaltrials.gov

B: Data reported for both panel A and panel B for ESK-NS 56 mg as stratified data on panel A and panel B is not reported at clinicaltrials.gov

During the follow-up phase a total of 3 ESK-NS treated patients had a serious adverse event. One patient (1 of 12) in the ESK-NS 28 mg group had a serious adverse event (confusional state), one patient (1 of 39) in ESK-NS 56 mg group had a serious adverse event (completed suicide) and one patient (1 of 42) in the ESK-NS 84 mg group had a serious adverse event (general physical health deterioration).(26)

Discontinuation due to adverse events

Three of 56 (5%) ESK-NS patients during the double-blind phase (compared with none receiving placebo) and 1 of 57 (2%) during the open-label phase had adverse events leading to discontinuation of the study drug (1 event each of syncope, headache, dissociative syndrome, and ectopic pregnancy).(26)

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

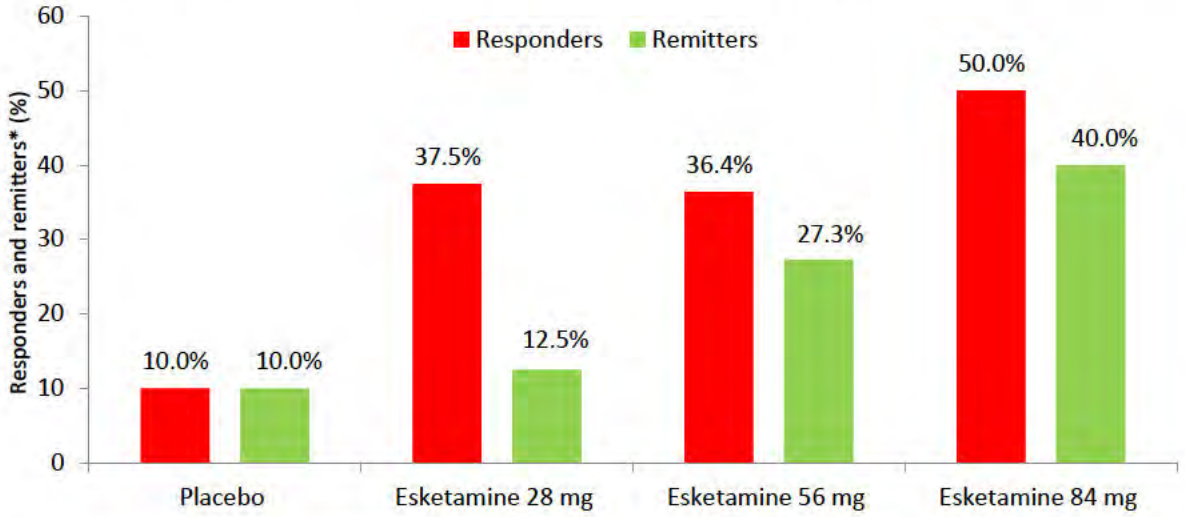
Remission and Response

For patients in the Period 1 and Period 2 ITT analysis sets, the percentages of responders in the esketamine treatment groups were generally greater than the percentages of responders in the placebo group after 1 week of treatment. At the Period 1 endpoint, 6.1% (2/33) of patients in the placebo group were considered responders. The following percentages of patients were considered responders in the esketamine groups: 9.1% (1/11) of patients in the 28 mg group, 18.2% (2/11) of patients in the 56 mg group, and 41.7% (5/12) of patients in the 84 mg group. At the Period 2 endpoint, none of the patients (0/6) reassigned to the placebo group were considered responders. For patients reassigned to esketamine treatment, the following percentages were considered responders: 12.5% of patients (1/8) in the 28 mg group, 0% (0/9) in the 56 mg group, and 20.0% (1/5) in the 84 mg group.(26)

For patients who received the same treatment for both periods and completed the double-blind phase, higher response rates (defined as ≥50% improvement from baseline in MADRS total score) were observed with esketamine nasal spray compared with placebo nasal spray, with 37.5%, 36.4% and, 50% of patients achieving a response at endpoint in the esketamine nasal spray 28 mg, esketamine nasal spray 56 mg and esketamine nasal spray 84 mg groups, respectively, while only 10% achieved a response in the placebo nasal spray group, see figure 18.(26)

Remission, as defined by a MADRS total score of ≤10 at endpoint (due to the difference in trial population, in Phase III trials where all patients have TRD, remission is defined as a MADRS total score of ≤12 at the end of the 4-week double-blind induction phase), was achieved in a progressively greater proportion of patients as the dose of esketamine nasal spray increased; 12.5%, 27.3% and 40% of those in the esketamine nasal spray 28 mg, esketamine nasal spray 56 mg, and esketamine nasal spray 84 mg groups achieved remission, respectively, compared with 10% of the placebo nasal spray group, see figure 18.(26)

Figure 18: Responders and Remitters at Endpoint for Patients Who Completed the Double-Blind Phase and Received the Same Treatment for Both Periods, Panel A, ITT (DB) Analysis Set (26)



* Response is defined ≥50% improvement from baseline in MADRS total score, remission is defined as a MADRS total score of ≤10 at endpoint

Quality of life

No published evidence is available on mean change from baseline EQ-5D-5L HSI.

6.1.10 ATU

The ATU results are reported for a cohort of adults with treatment-resistant Major Depressive Disorder who have not responded to at least two different treatments with antidepressants of two different classes in the current moderate to severe depressive episode with contraindication to electroconvulsive therapy (ECT), without access to ECT, resistant to ECT, or who refuse ECT.(35-37) Consequently, this should be kept in mind when assessing the result reported for the ATU cohort. The results for ATU cohort are summarized in table A3h of section 8.2 in the appendix.

Serious adverse events

Among all the patients treated during the ATU, eight (8) patients experienced serious adverse reactions. The cases associated with these 8 patients are summarized in the table 39 below.(37)

Table 39: Serious adverse events (35, 36)

Serious adverse events	Expected side effects[a]	Unexpected side effects
Altered state of consciousness	0	1
Balance disorder	0	1
Lethargy	1	0
Sedation	1	0
Anxiety	1	0
Depersonalization	1	0
Visual hallucination	1	0
Suicidal ideation	3	0
Suicide attempt	0	1
Skin eruption	0	1
Hypertension	1	0

[a]Expected side effects = related to stopping esketamine nasal spray solution for ≥ 2 patients in phase 3 studies

Of the eight (8) patients with serious adverse reactions, four (4) patients had suicidal ideations or suicide attempt. Regarding the 4 other patients: one patient had a serious visual hallucination. The three (3) other patients experienced altered state of consciousness, marked dissociative state and arterial hypertension / sedation and lethargy, or depersonalization and anxiety.(35, 36)

Discontinuation due to adverse events

Among all the patients treated during the ATU, 25 patients stopped treatment, an average of 44.0 days after initiation of treatment. Of the 25 patients who stopped treatment, 24 had a treatment discontinuation record. Eight 8 (33.3%) patients stopped for adverse effect: Suicidal ideation, reappearance symptomatic of a post traumatic disorder, depersonalization derealization, anxiety, sedation and dissociation. Whereas 14 (58.3%) stopped due to insufficient therapeutic effect and 2 stopped due to patient´s wish to discontinue treatment. (35, 36)

Narrative review of specific incidents, death for whatever reason and suicide attempts

No deaths occurred during the ATU, however see section 6.1.12 for a narrative description the of suicide attempt and suicidal ideation that occurred.

Remission and Response

No evidence is available on remission and response

Quality of life

No evidence is available on remission and response

6.1.11 TRD cohort study

Results for the Treatment Resistant Depression Cohort in Europe study on the baseline socio-demographic, disease- and treatment-related characteristics, social and work-related burden as well as treatment patterns and clinical outcomes are reported in two published studies by Heerlein. K., et al. 2021.(15, 29) However, to answer the clinical question and provide data on efficacy outcomes of interest as stated by the Scientific Committee, only post-hoc analyses on MADRS total score change from baseline, response and remission results at 6 months are presented as they constitute the basis of an indirect treatment comparison between the SUSTAIN-2 study and the TRD cohort study. The results for the TRD cohort are summarized in table A3i of section 8.2 in the appendix and the post-hoc analysis method as well as method of the indirect treatment comparison is available in section 8.5.1.

It is important to be aware of the differences in data processing and statistical analyses if comparing results from the published Heerlein et al. 2021 study with the post-hoc analyses results presented in this dossier. These distinctions are outlined in table 40 beneath.

Table 40: Data processing and statistical analyses differences between the Heerlein et al. 2021 study and the post-hoc analyses of the TRD cohort.(15, 30)

	Heerlein et al 2021	Post-hoc analyses
Definitions of visits considered as occurring in month 6	Visits were considered as occurring in Month 6 if they occurred 150–216 days after enrollment, while Month 12 visits were defined as those occurring 330–402 days after enrolment. Data obtained outside these windows were excluded from the relevant time point.	For the patients in the TRD observational cohort study, patients who did not have a registered visit in the month 6 time window (day 150-216), but with a recorded visit after the month 6 window (thus, a visit after day 216 post-baseline), these patients were also considered for the analysis.
Patients included in the analyses	The analysis is on a patient population (N=306) remaining after having excluded 58 patients which were reported as discontinued and 47 patients who were still in the study at month 6, but whose visit did not meet the defined cut-off dates for a month 6 visit. Analyses were performed on patients in the TRD cohort irrespectively of which baseline therapy they received.	In the TRD observational cohort study, NRI was implemented 1) for patients that dropped out of the study before reaching the month 6 timepoint, as well as 2) for patients who, between baseline and month 6, changed their treatment strategy in a way which could be suggestive for a treatment failure. Specifically, treatment stop (stopping an antidepressant and not initiating a new one), treatment switch (stopping an antidepressant A and starting an antidepressant B), treatment combination (adding antidepressant B on top of antidepressant A) and treatment augmentation (adding augmentation substance X on top of antidepressant A) were considered cases of treatment failure and led to implementation of NRI. Of note, combination stop and an augmentation stop were not considered suggestive of treatment failure and did not lead to NRI. Furthermore the post-hoc analyses were performed on patients in the TRD cohort who received at least one oral antidepressant therapy at baseline.
Remission and Response	The MADRS values at the start and end of each treatment strategy were used to determine whether the	Binary endpoints analysed were response rates at month 6 (MADRS % improvement of at least 50% relative to study baseline), remission rates at month 6 (MADRS≤10).

	patient had experienced remission, response without remission, or no response. When the MADRS score was not available, a response/remission proxy was inferred based on CGI scores, to increase the number of treatment strategies for which a corresponding treatment outcome could be reported.	

MADRS total score at 6 months

The post-hoc analyses showed that the mean MADRS total score decreased from baseline to endpoint at 6 months with a mean change from of [redacted] reported for patients treated in the TRD cohort study, see table 41.(40)

[redacted]

Serious adverse events

No evidence is available on serious adverse events, however Heerlein et al. 2021 reported that 4 died at month 12. (15)

Discontinuation due to adverse events

No evidence is available on discontinuation due to adverse events.(15, 29)

Narrative review of specific incidents, death for whatever reason and suicide attempts

A narrative review of specific incidents, death for whatever reason and suicide attempts is not possible as no evidence is available on safety and the reasons for the 4 death are not reported.(15)

Remission and Response at 6 months

The post-hoc analyses on response at 6 months showed that the proportion of patients with response based on the MADRS total score (response defined as ≥50% reduction, ie, improvement from baseline of the induction phase), was [redacted] In addition, the proportion of patients with remission based on the MADRS total score (remission defined as MADRS total score ≤10), was [redacted] at 6 months, see table 42.(40)

Table 42: Summary of Treatment Resistant Depression Cohort in Europe study post-hoc analyses on response and remission results at 6 months

[redacted]

Quality of life

Heerlein et al. 2021 reported evidence on EQ-5D-5L (change from baseline) at month 6. For patients with no response the mean (SD) change from baseline was 0.11 (0.25) whereas patients having a response without remission had a mean change of 0.26 (0.21) and patients with remission had a mean change of 0.34 (0.26).(15)

6.1.12 Narrative review of specific incidents, death for whatever reason and suicide attempts

Death for other seasons than suicide

In the primary safety analysis set across the included phase 3 studies in TRD, there was 1 death among patients with ESK-NS + OAD and no deaths occurred in the OAD + PBO-NS groups in the double-blind phase, see table 43. The 4 remaining deaths in the ESK-NS + OAD occurred in the open-label safety studies SUSTAIN-2 and SUSTAIN-3 without a comparator. (1)

Table 43: Overview of deaths observed in the included studies of this application.(1)

Subject Number (Study)	Age Sex	Dictionary-derived Term (Reported Term)	Study Day of Onset	Protocol Phase	Onset Dose	Investigator's assessment of Relationship
COMPLETED STUDIES						
Phase 3 TRD Studies (esketamine + newly initiated oral AD)						
TRANSFORM-2	41 Male	Multiple injuries (Multiple injuries following a road traffic accident)	16[b]	DB	<84>	Not related
SUSTAIN-2	60 Male	Acute Respiratory Failure (Acute Respiratory Failure) Cardiac Failure Acute (Acute Heart Failure) (	113 113	Optimization/ Maintenance Optimization/ Maintenance	<56> <56>	Doubtful Doubtful
SUSTAIN-3	73 Female	Myocardial Infarction	321	Optimization/ Maintenance	<84>	Doubtful
SUSTAIN-3	59 Male	Polytrauma (Accidental)	364	Optimization/ Maintenance	<56>	Not related
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Data from Abbreviated Interim #2 Clinical Study Report of SUSTAIN-3

In regards to TRANSFORM-2, one patient in the ESK-NS + OAD group experienced multiple injuries following a road traffic (motorbike) accident on day 16 of the double-blind phase and subsequently died on day 55, 40 days after the last dose of esketamine. The motor vehicle accident with fatal outcome occurred ~28 hours after the patient's last dose of esketamine. Information on drug levels at the time of death is not available, as it was not collected in the emergency room. This patient underwent pre-dose cognitive testing evaluation, which included reaction time measurement on the day of the final dosing preceding the accident, with normal results. The patient did not experience other adverse events. No history of suicidal behavior and no suicidal ideations (C-SSRS was 0 at all timepoints) were reported. In the SAE report narrative provided by the site, the verbatim description of the event was: "The accident was not patient's fault, but he ended up falling down and hitting a tree." The investigator assessed the road traffic accident

as doubtfully related to esketamine or antidepressant. An autopsy was performed, however the report was not shared with investigator or Sponsor based on the family's wishes. (32)
The Sponsor's internal Safety Management Team (a product-based, cross-functional collaborative team responsible for review, assessment, and evaluation of Medical Safety data arising from any source) also reviewed the case as part of the Safety Oversight and, based on the available evidence, considered it not related to the study treatment. Similarly, the case was reviewed by an Independent Data Monitoring Committee (IDMC) established for the esketamine phase 3 TRD studies
Esketamine has a short half-life and is rapidly cleared from the plasma (which tightly parallels the rates of the drop in brain concentrations and receptor occupancy), therefore it seems unlikely that esketamine played a role in this accident. Moreover, we conducted two formal studies of the effects of esketamine nasal spray on driving, which supported the safety of driving on the day following esketamine dosing. Per protocol, patients were discharged from the clinical site accompanied by a responsible adult and were not allowed to drive a car or operate machinery within 24 hours following an intranasal session. (32)

In SUSTAIN-2, there were one death, for other reasons than completed suicide, assessed as doubtful related to esketamine by the investigator, during the optimization/maintenance phase of the study (acute cardiac failure and acute respiratory failure in one).(33) The one subject, a 60-year-old man, who had a medical history of hypertension, right lower limb vein surgery, and was treated with candesartan cilexetil, died on Day 113 of the study (last dose of esketamine was Day 108). The death was due to acute cardiac and respiratory failure that were both considered doubtfully related to esketamine treatment. This subject did not report prior cardiac adverse events, tolerated treatment with esketamine (56 mg) and sertraline (150 mg), and had normal blood pressure during the study.(33)

In SUSTAIN-3, there were 3 subjects who died, for other reasons than completed suicide, during the optimization/maintenance phase. The events were considered by the investigator as doubtfully related (n = 1) or not related (n = 2) to esketamine nasal spray treatment.(1, 24) A narrative review are available in the following paragraph.

[redacted]

Death due to completed suicide

Although death by suicide is always tragic, in the ESK-NS TRD development program, the suicide completion rate (0.49 per 100 patient-years of treatment) was comparable to the background rate of 0.47 (95% CI: 0.22-1.00) completed suicides per 100 patient-years reported in a different study in a TRD population (Drevets 2019; Bergfeld 2018). After extensive review by study site investigators, none of the suicides were deemed related to ESK-NS. Additionally, safety data was reviewed every 6 months by an Independent Data Monitoring Committee (IDMC) to ensure the continuing safety of the patients enrolled in the phase 3 trials (43).

In the 6 completed Phase 2 and 3 studies, there were 2 confirmed cases of completed suicide among the 1,708 subjects treated with ESK-NS (cumulative exposure of 611 patient-years). No cases of completed suicide were reported in 432 subjects who received oral AD + placebo (cumulative exposure of 107 patient-years) [redacted]

[redacted]

[redacted]

Table 44: Serious Adverse Events of Completed Suicides in Clinical Studies of ESK-NS in TRD.(24, 44).

Study	Age (years)/gender	Narrative	Investigator's Assessment of relationship to esk-ns
[redacted]			

Suicidal ideation

Suicidal ideation is a major and frequently precondition of suicidal behaviour observed in people with depression. Short-term studies have reported an increased risk of suicidal thoughts and behavior in pediatric and young adult patients treated with antidepressants.(45) In subjects with TRD, it is important to determine the effect of treatment on the risk of experiencing a suicide-related event. An evaluation was conducted to identify the occurrence of potentially suicide-related events in the esketamine clinical trial program. This assessment involved a review of the data based on the Columbian-Suicide Severity Rating Scale (C-SSRS), as well as incidence, type and, severity of suicidality-related AEs and clinical evaluation of individual cases.

C-SSRS was used to prospectively assess potential suicidal ideation and behavior in the ESK-NS clinical trial program in patients with TRD. Patients with suicidal ideation were not excluded in the trials; however, subjects with a recent history or current significant suicidal ideation with some intent to act within the prior 6 months (per the investigator's clinical judgment and/or based on the C-SSRS), or suicidal behavior within the past 1 year were excluded from the Phase 2 and 3 TRD studies(43, 44).

In the Phase 3 studies, between 25% and 37% of subjects across studies/treatment groups had a lifetime history of suicidal ideation as assessed using the C-SSRS, and 14% to 19% had a lifetime history of suicidal behavior. Based on the last C-SSRS score taken during the period between screening and Day 1, suicidal ideation at baseline was reported for 17.1% to 25.3% of subjects in the ESK-NS + OAD group and 16.9% to 27.0% of subjects in the OAD+PBO-NS group in the short-term studies (44).

Across all Phase 3 studies, suicidal ideation (ie, C-SSRS score of 1-5) was reported at least once during the treatment period at similar rates in subjects receiving ESK-NS + OAD and those receiving OAD + PBO-NS. These scores were generally at the lower end of the score range (1-2). The proportion of subjects with suicidal ideation, as assessed using the C-SSRS, decreased from baseline in both treatment groups in the controlled studies in adults, indicating an overall trend towards a reduction in suicidal ideation. Suicidal behavior (ie, C-SSRS score of 6-10) was reported in 10 subjects who received ESK-NS + OAD and in no subjects who received only OAD + PBO-NS in the Phase 3 studies prior to the FU phase, table 45 (44).

Most subjects stayed within the same suicidality category throughout the duration of the Phase 3 studies. Worsening in subjects' suicidality categories at any time during the postbaseline treatment phase are summarized in table 45.

- In the subgroup of subjects with *no suicidal ideation or behavior at baseline*, the proportion of subjects reporting suicidal ideation at any time postbaseline was similar in the ESK-NS + OAD group and in the OAD + PBO-NS group during the DB IND phase of the pooled short-term studies (TRANSFORM-1/2: 10.2% vs. 12.3%) and short-term elderly study (TRANSFOMR-3: 13.8% vs. 16.7%), and in the DB MA phase of the relapse-prevention study (SUSTAIN-1: 2.4% vs. 4.5%). Only a small number of subjects in this subgroup, all of whom had ESK-NS exposure, had suicidal behavior at any time postbaseline (1 [0.3%] subject in the IND phase of SUSTAIN-1; 2 [0.3%] subjects in IND phase of SUSTAIN-2, and 2 [0.4%] in the OP/MA Phase of SUSTAIN-2) (44).

- In the subgroup of subjects with *suicidal ideation at baseline* across all Phase 3 studies, a total of 5 subjects, all of whom received ESK-NS, reported suicidal behavior at any time postbaseline: 1

(1.2%) subject in the ESK-NS + OAD group in the pooled short-term studies TRANSFORM-1/2 and 4 subjects in SUSTAIN-2 (2 [1.6%] during the IND phase and 2 [2.2%] in the OP/MA Phase) (44).

All subjects who reported suicidal behavior during the Phase 3 studies had a lifetime history of suicidal ideation or suicidal behavior. In addition, most of the subjects who had a clinically significant suicidal ideation score (ie, maximum postbaseline C-SSRS score of 4 or 5) during treatment with ESK-NS + OAD also had suicidal ideation at baseline. Consistent with the Phase 3 studies, subjects enrolled in the Phase 2 SYNAPSE study had a significant history of ideation and behavior. (44)

[redacted]

Table 45: Subjects Who Had a Worsening in Suicidality Based on the C-SSRS in Completed Phase 3 TRD studies. (44)

		Subjects with No Suicidal Ideation or Behavior (no Event) at Baseline			Subjects with Suicidal Ideation at Baseline	
Study Phase	Treatment (+ Oral AD)	N	*n (%) with Suicidal Ideation at any time postbaseline*	*n (%) with Suicidal Behavior at any time postbaseline*	N	*n (%) with Suicidal Behavior at any time postbaseline*
TRANSFORM-1 (Fixed-dose)						
Induction Phase	Esk 56 mg:	87	12 (13.8%)	0	28	1 (3.6%)
	Esk 84 mg:	78	8 (10.3%)	0	35	0
	Placebo:	77	13 (16.9%)	0	36	0

TRANSFORM-2 (Flex-dose)						
Induction Phase	Esk 56-84 mg:	89	6 (6.7%)	0	23	0
	Placebo:	85	7 (8.2%)	0	24	0
Pooled TRANSFORM-1/2						
Induction Phase	Total Esk[a]:	254	26 (10.2%)	0	86	1 (1.2%)
	Total Placebo:	162	20 (12.3%)	0	60	0
TRANSFORM-3						
Induction Phase	Esk 28-84 mg:	58	8 (13.8%)	0	12	0
	Placebo:	54	9 (16.7%)	0	11	0
SUSTAIN-1						
Induction Phase	Esk 56-84 mg:	362	41 (11.3%)	1 (0.3%)	62	0
OP Phase	Esk 56-84 mg:	387	22 (5.7%)	0	64	0
MA Phase	Esk 56-84 mg:	126	3 (2.4%)	0	25	0
	Placebo:	133	6 (4.5%)	0	12	0
SUSTAIN-2						
Induction Phase	Esk 28-84 mg:	637	71 (11.1%)	2 (0.3%)	124	2 (1.6%)
OP/MA Phase	Esk 28-84 mg:	509	59 (11.6%)	2 (0.4%)	93	2 (2.2%)

Note: For each study, each subject is counted only once in the above table, based on the most severe postbaseline C-SSRS category: No event=0; Suicidal ideation =1, 2, 3, 4, 5; Suicidal behavior =6, 7, 8, 9, 10.

[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

Baseline is 7 days prior to enrollment/randomization.

[redacted]

Adverse events

The search for events potentially related to suicidality included the following PTs: *Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt.*

The overall incidence of these TEAEs in the completed Phase 3 studies is summarized in Table 47.

- In the pooled short-term studies TRANSFORM-1 and TRANSFOMR-2, 3 (0.9%) subjects in the total ESK—NS + OAD group and 2 (0.9%) subjects in the OAD + PBO-NS group reported a suicidality-related TEAE during the DB Phase. These events included PTs of suicidal ideation (n=2 subjects in the ESK-NS + OAD group and n=1 in the OAD + PBO-NS group) and intentional self-injury (n=1 in each group) (44).
- In the short-term study in the elderly TRANSFOMR-3, during the DB phase 1 (1.4%) subject in the ESK-NS + OAD group and no subjects in the OAD + PBO-NS group reported a suicidality-related TEAE. The TEAE coded to the PT of suicidal behavior in the one subject was considered by the investigator as mild and not related to either study medication. Subsequent FU clarified that the subject experienced a worsening of suicidal thoughts without intent, rather than suicidal behavior (maximum postbaseline C-SSRS score of 4)(44).
- In the IND and OP phases of relapse prevention study SUSTAIN-1, a total of 5 (1.1%) subjects in the IND phase and 1 (0.2%) subject in the OP phase reported a suicidality-related TEAE. These events included suicidal ideation in 3 (0.7%) subjects, intentional self injury in 1 (0.2%) subject, and suicidal behavior in

1 (0.2%) subject during the IND phase, and suicidal ideation (in 1 [0.2%] subject) during the OP phase(44).

- In the DB MA phase of relapse prevention study SUSTAIN-1, 3 (2.0%) subjects in the ESK-NS + OAD group and 1 (0.7%) subject in the OAD + PBO-NS group reported a suicidality-related TEAE. These events included PTs of suicidal ideation (n=1) and intentional self injury (n=2; reported term of "self-injury, superficial burns" noted as non-suicidal self-injurious behavior on the C-SSRS; and reported term of "superficial cut in right arm, without suicidal intent for relief of distress symptom") in the ESK-NS- + OAD group, and suicidal ideation (n=1) in the OAD + PBO-NS group (44).
- In the OL long-term safety study SUSTAIN-2 (IND and OP/MA phases combined), 42 (5.2%) subjects reported a suicidality-related TEAE, the most common of which was suicidal ideation (n=26 [3.2%]). Other PTs were each reported by <1% of subjects (intentional self injury [n=7, 0.9%], suicide attempt [n=7, 0.9%], suicidal behaviour [n=3, 0.4%], completed suicide [n=1, 0.1%], and depression suicidal [n=1, 0.1%])(44).
- In the Phase 2 study SYNAPSE (Panel A and B combined), no subjects in the esketamine treatment group and 1 (1.9%) subject on placebo reported a suicidality-related TEAE during the DB Phase. In the OL phase, 2 (2.1%) subjects reported a TEAE of suicidal ideation; both of these events were of mild

[redacted]

Table 47: Overall Incidence of Treatment-emergent Adverse Events in the Category of Suicidality in Completed Phase 3 TRD Studies. (44)

Study Phase	Treatment (+ Oral AD)	N	Any TEAE related to Suicidality
TRANSFORM-1(Fixed-Dose)			
Induction Phase	Esk 56 mg:	115	1 (0.9%)
	Esk 84 mg:	116	2 (1.7%)
	Placebo:	113	1 (0.9%)
TRANSFORM-2 (Flex-Dose)			
Induction Phase	Esk 56-84 mg:	115	0 (0%)
	Placebo:	109	1 (0.9%)

Pooled - TRANFORM-1/TRANSFORM-2			
Induction Phase	Total Esk[a]:	346	3 (0.9%)
	Total Placebo:	222	2 (0.9%)
TRANFORM-3			
Induction Phase	Esk 28-84 mg:	72	1 (1.4%)
	Placebo:	65	0 (0%)
SUSTAIN-1			
Induction Phase	Esk 56-84 mg:	437	5 (1.1%)
Optimization (OP) Phase	Esk 56-84 mg:	455	1 (0.2%)
Maintenance (MA) Phase	Esk 56-84 mg:	152	3 (2.0%)
	Placebo:	145	1 (0.7%)
SUSTAIN-2			
Induction Phase	Esk 28-84 mg:	779	19 (2.4%)
OP/MA Phase	Esk 28-84 mg:	603	23 (3.8%)
Induction and OP/MA Phases	Esk 28-84 mg:	802	42 (5.2%)

Note: TEAEs in the category of suicidality included *Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt*. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

Suicidality-related TEAEs were reported as severe in only a small number of subjects. In the pooled short-term studies TRANSFORM-1/2, 1 (0.3%) subject in the ESK-NS + OAD group (and no subjects in the OAD + PBO-NS group) reported a severe suicidality-related TEAE (suicidal ideation) during the DB phase. No severe suicidality-related TEAEs were reported in esketamine-treated subjects in the DB phase of the elderly study TRANSFORM-3, or the DB or OL Phases of the Phase 2 study SYNAPSE. In the relapse prevention study SUSTAIN-1, 1 (0.2%) subject reported a severe suicidality-related TEAE in the IND Phase (suicidal ideation); no severe events were observed in the OP or MA phases. In the long-term safety study SUSTAIN-2, severe suicidality-related TEAEs included suicide attempt (in 7 [0.9%] subjects), completed suicide (in 1 [0.1%] subject), and suicidal ideation (in 5 [0.6%] subjects; ie, most of the subjects with a TEAE of suicidal ideation [n=26] had mild or moderate events).

Based on clinical review, most suicidality-related TEAEs were considered either not related or doubtfully related to esketamine treatment in the opinion of the investigator and therefore likely associated with the underlying disease. Most events resulted in no change to the intranasal study medication and resolved without intervention/hospitalization.

Suicidality-related TEAEs were reported as SAEs and/or led to treatment discontinuation at low rates (44).

- In the short-term studies in adults (TRANSFORM-1/2) and elderly subjects (TRANSFOMR-3), no SAEs or discontinuations due to suicidality-related TEAEs were observed during the DB phase(44).
- In the relapse prevention study SUSTAIN-1, 1 (0.2%) subject reported a SAE of suicidal ideation during the IND phase(44):
  - A subject reported suicidal ideation on Day 8 of the IND phase considered by the investigator to be very likely related to esketamine and resulting in withdrawal of treatment. The subject reported unusual gastrointestinal dissociative symptoms during the post dose period and it was during this period that the subject. There was no evidence of psychosis. The Sponsor considered the event of suicidal ideation as not related to ESK-NS but instead related to the underlying major depressive disorder.
  - One other subject reported a SAE of suicidal ideation on Day 47 post-study, after failing to meet the criteria for continuing to the next study phase (last dose of esketamine was on Day 25). This was considered not related to ESK-NS.
- In the long-term safety study SUSTAIN-2 (across phases), suicidality-related SAEs included: suicidal ideation and suicide attempt (each reported in 6 [0.7%] subjects), depression suicidal, and intentional self-injury (each reported in 1 [0.1%] subject), and 1 completed suicide. All SAEs resolved/recovered, except for the completed suicide that resulted in death. (44).
  - All suicidality-related SAEs were considered by the investigator to be of no relationship or of doubtful relationship to ESK-NS, with the exception of 2 events which were considered of probable relationship to ESK-NS (a moderate event of suicidal ideation on Day 207, and a severe event of suicidal attempt on Day 48).
  - A total of 10 subjects in SUSTAIN-2 were withdrawn from treatment due to a suicidality-related TEAE, including 7 (0.9%) subjects with suicidal ideation, 2 (0.2%) subjects with suicide attempt, and 1 (0.1%) subject with depression suicidal. All these events were SAEs, with the exception of 2 non-serious events of suicidal ideation.
- In the Phase 2 study SYNAPSE, no suicidality-related TEAEs were serious or led to discontinuation of intranasal treatment during the DB or OL Phases. During the FU phase, 1 subject in Panel B died due to

completed suicide, 20 days after receiving the last dose of study medication (Subject in the SYNAPSE

[redacted]

Suicidality-related TEAEs were also analyzed by age group. Since the number of subjects in the category of potential interest based on the literature (18 to 25 years) was too low, the youngest age group for this evaluation was defined as 18 to 44 years. Overall, there was no difference in the incidence or types of suicidality-related TEAEs between subjects aged 18 to 44 years or 45 to 64 years in the pooled short-term studies (TRANSFORM-1/2) or during the IND, OP or MA phases of the relapse-prevention study (SUSTAIN-1), or between subjects aged 65 to 74 years and ≥75 years in the short-term study in elderly subjects (TRANSFOMR-3). However, the overall reporting of suicidality-related TEAEs in these studies was low (see table 47). In the long-term OL study (IND and OP/MA phases combined), suicidality-related TEAEs were reported in 19 of 225 subjects (8.4%) aged 18 to 44 years, 22 of 399 subjects (5.5%) aged 45 to 64 years, 1 of 138 subjects (0.7%) aged 65 to 74 years, and 0 of 17 subjects aged ≥75 years (44). [redacted]

In addition to the suicide related TEAEs observed in the clinical trials for ESK-NS+OAD which have been described above, a narrative description of suicide attempt and suicidal ideation observed in the ATU are given in bullets in the following.(28)

[redacted]

[redacted]

- [redacted]

[redacted]

Dissociation

Dissociation is one of the most commonly reported psychomimetic adverse event of ketamine (47) and an important identified risk with intranasal esketamine. The literature has also reported a potential acute effect of ketamine on psychotic symptoms in healthy volunteers and recreational ketamine users (48, 49), while no evidence of clinical psychotic symptoms in infrequent ketamine users has been described (50). The esketamine phase 2 and 3 program included the CADSS scale for assessment of dissociative/perceptual changes. Dissociative/perceptual changes; are a selected safety topic of interest that were comprehensively examined in the clinical trial program of esketamine. Further, dissociation was included in the RMP as an important identified risk for ESK-NS.

CADSS score

Across completed Phase 2 and 3 studies, the most common psychological effects of ESK-NS were dissociative/perceptual changes (including distortion of time and space and illusions), derealization and depersonalization captured using the Clinician Administered Dissociative Symptoms Scale (CADSS) rating scale. The total CADSS score ranges from 0 to 92, with a higher score representing a more severe condition. Scores between 0 and 4 are considered to be in the normal range.

An increase in CADSS total score was observed in a high proportion of subjects in the ESK-NS + OAD group in the short-term DB studies TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3 (ranging from 89.5% to 93.1%), indicating an increase in the dissociative state (ie, more severe condition). Despite the expectation that dissociative symptoms would be reported only in the esketamine-treated subjects, a substantial number of subjects in the OAD + PBO-NS group (28 to 40%) also experienced these symptoms.

In the relapse-prevention study SUSTAIN-1, an increase in CADSS total score was observed in 85.1% of esketamine-treated subjects in the IND phase, 70.5% during the OP phase, and 77.5% during the MA phase (compared with 18.9% of subjects in the OAD + PBO-NS group). In the long-term OL study SUSTAIN-2, an increase in CADSS total score was observed in 92.0% during the IND phase and 86.1% during the OP/MA phase.

In the fixed-dose study TRANSFORM-1, increases in CADSS total score from baseline were reported at a higher rate in the ESK-NS 84 mg + OAD group (93.1%) than in the ESK-NS 56 mg + OAD group (87.8%) (compared with 28.3% in the OAD + PBO-NS group). In the adjunctive Phase 2 study SYNAPSE, there also was evidence of a dose response in both Panel A and Panel B.

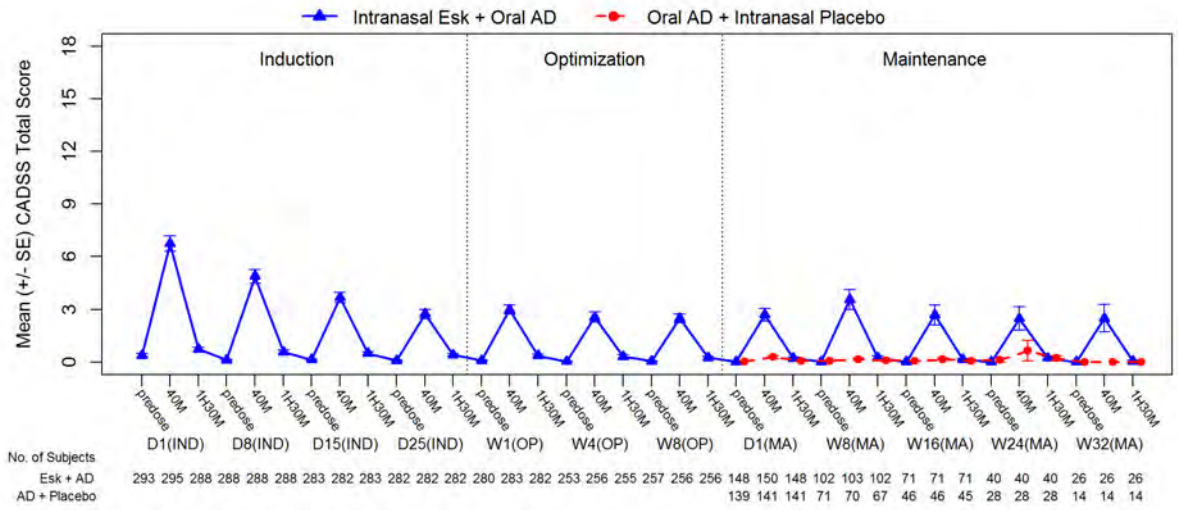
Based on the changes in mean CADSS score over time observed consistently in each dosing session, the dissociative/perceptual changes had an onset shortly after the start of the dose, peaked by 40 minutes postdose (with maximum mean values not exceeding 10) and typically resolved by 1.5 hours postdose in line with the PK profile of ESK-NS.

Over the course of treatment across the studies, the peak mean CADSS total score at the 40-minute post-dose time-point in subjects treated with ESK-NS + OAD generally decreased with consecutive doses. This attenuation was apparent both in the short-term studies as well as with prolonged exposure in the long-term studies (see Figure 19a and 19b for the long-term studies SUSTAIN-1 and SUSTAIN-2, respectively). No postdose CADSS scores were considered clinically significant at any time point in the OP or MA (SUSTAIN-1) or OP/MA (SUSTAIN-2) phases, with mean values generally less than 3.

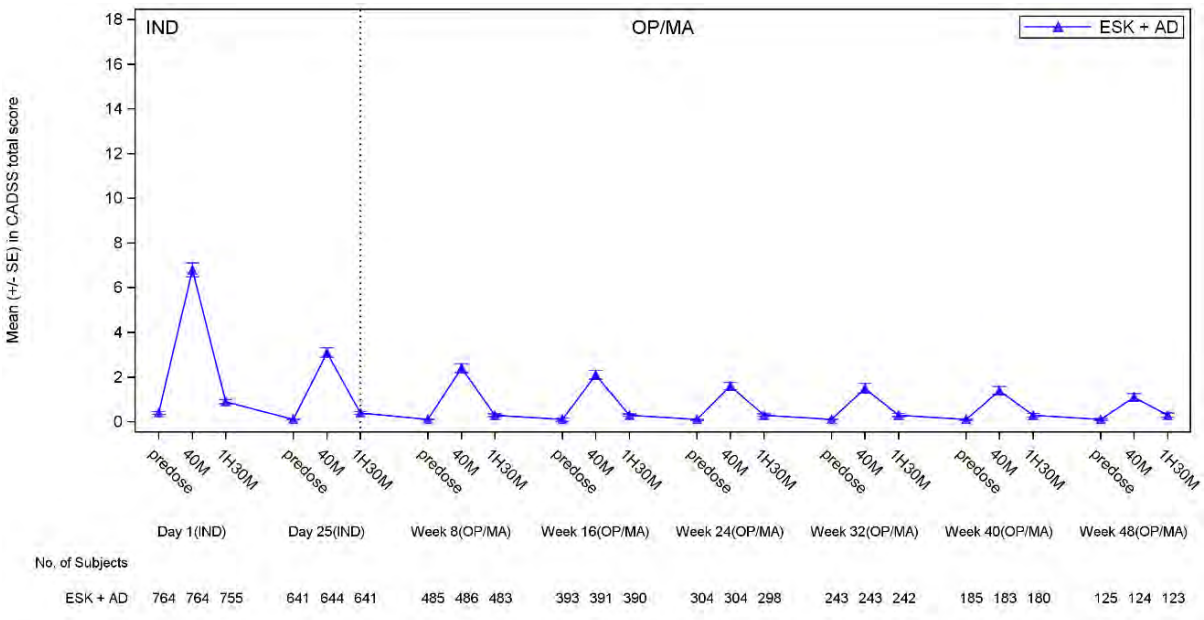
Clinical review identified rare instances in individual subjects where after a period of apparent attenuation of symptoms, there was a sporadic increase in symptoms at one dosing session for no obvious reason. Generally, these events were rare, not considered as clinically meaningful, and did not tend to recur for individual patients.

Figure 19: Mean Total CADSS Score over Time in the Long-Term Phase 3 Studies

A. Study SUSTAIN-1, safety (MA) Analysis Set



B. Study SUSTAIN-2: All Enrolled Analysis Set



NOTE: data for the IND phase of SUSTAIN-1 originate from TRANSFORM-1/2 for the transferred-entry subjects

A PK/PD model was used to describe the relationship between CADSS scores and ESK-NS plasma concentrations. The incidence of CADSS scores >4 at 40-minutes postdose (i.e. close to the time of maximum plasma esketamine concentrations) over the course of an initial 4-week treatment with ESK-NS was described using a logistic regression model. The results demonstrated that the effects of ESK-NS are dose-dependent and the tolerance to the dissociative effects of ESK-NS develops. For example, the model predicted incidence of CADSS>4 on Day 1 at 40 min after intranasal administration of esketamine is 46.0% (95% CI: 42.6; 49.5) and 55.6% (95% CI: 51.4; 60.0) for the 56-mg and 84-mg, respectively. The model predicted incidence on Day 25 (ie, after 4 weeks of treatment) is 22.1% (95% CI: 19.9; 24.3) and 24.8% (95% CI: 22.2; 27.7), respectively.

Adverse events (dissociative effects)

There was no universal profile of dissociative symptoms associated with ESK-NS. Dissociation included delusional perception, depersonalization/derealization disorder, derealization, diplopia, dissociation, dysesthesia, feeling cold, feeling hot, feeling of body temperature change, hallucination, hallucination-auditory, hallucination- visual, hyperacusis, illusion, ocular discomfort, oral dysesthesia, paresthesia, paresthesia oral, pharyngeal paresthesia, photophobia, time perception altered, tinnitus, vision blurred, and visual impairment. However, symptom clusters including changes in bodily sensations, general perceptual changes, and a general sense of being disconnected from one's own experience (depersonalization) increased in frequency as the severity of clinician reported adverse events of dissociation increased (51)

In the completed Phase 2 and 3 studies, the transient dissociative/perceptual changes were most often reported as TEAEs of dissociation, feeling abnormal, and feeling drunk. The events of feeling abnormal and feeling drunk across studies were mostly reported at incidences under 5% and were rarely severe in intensity.

Dissociation was one of the most common individual TEAEs associated with ESK-NS administration across studies. In the pooled short-term studies TRANSFORM-1/2, rates of dissociation in ESK-NS treated subjects were 26.6% as compared with 3.6% in the OAD + PBO-NS group, and 12.5% vs. 1.5% in the short-term elderly study (TRANSFORM-3) (table 48).(16, 18, 19) The reporting rates in ESK-NS treated subjects were in the relapse prevention study SUSTAIN-1 18.8% in IND phase, 16.0% in OP phase, and 23.0% in the MA phase (no reports in subjects in the OAD + PBO-ns group in MA phase) and 27.6% across phases in the long-term safety study SUSTAIN-2.(17, 33) A similar rate (17.9%) was observed in the phase 2 study SYNAPSE.(26) [redacted]

TEAEs of dissociation were primarily mild or moderate in severity. Severe TEAEs of dissociation were reported in 13 subjects (3.8%) in the pooled short-term studies TRANSFORM-1/2 while none were reported in the elderly subjects in TRANSFORM-3. Severe TEAEs of dissociation occurred in 5 subjects (1.1%) in the IND phase, 5 subjects (1.1%) in the OP phase, and 1 subject (0.7%) in the MA phase of the relapse prevention study SUSTAIN-1 and in 15 subjects (1.7%) across phases in the long-term safety study SUSTAIN-2 (of note, 11 of these 14 severe events were reported in the IND phase) (Table 29). [redacted] In the phase 2 study SYNAPSE, no severe TEAEs of dissociation were reported.

The overall rate of TEAEs of dissociation (ESK-NS 56 mg: 17.4%; ESK-NS 84 mg: 23.8%) and the rate of severe TEAEs of dissociation (ESK-NS 56 mg: 1.7%; ESK-NS 84 mg: 6%) were reported higher in subjects receiving ESK-NS 84 mg than in subjects receiving ESK-NS 56 mg in the fixed-dose study TRANSFORM-1.

Reported rates of the TEAEs of dissociation decreased over time by intranasal dosing session in the pooled short-term studies TRANFORM-1/2. In the long-term studies SUSTAIN-1 and SUSTAIN-2, this attenuation in reporting frequency was most pronounced in the IND phase.

Nearly all TEAEs reflecting dissociative/perceptual changes were reported on the day of ESK-NS administration and resolved the same day. TEAEs of dissociation, including dissociation of severe intensity, were reported on the day of dosing in the ESK-NS treated subjects in >95% of cases across the

TRANSFORM-1/2/3 and SUSTAIN-1/2 studies, and resolved the same day except in a few isolated cases (Table 48). [redacted]

All reported TEAEs of felling drunk and feeling abnormal reported on the day of dosing resolved the same day across the Phase 3 studies. Further, consistent with the observations captured in the CADSS rating scale, the median duration of the TEAEs of dissociation, feeling abnormal, and feeling drunk across dosing sessions did not exceed 2 hours [redacted]

In a post-hoc analysis of TRANSFORM-1 and TRANSFORM-2 the correlation of incidence of dissociation (reported as an adverse event) during the first week of treatment was measured during week 2-4. Of the 345 patients who received ESK-NS + OAD, the incidence of dissociation was 26.6% over the 4 weeks of treatment. Results showed that if dissociation was not reported in week 1, <6% of patients experienced that adverse event after any subsequent treatments. In contrast, if patients had experienced dissociation during week 1 the likelihood of experiencing dissociation during the subsequent 3 weeks of treatments were high (71.4% if experienced once during week 1, and 94.0% if experienced twice during week 1) (table 49) (52). A similar post hoc analysis was conducted for the long-term studies that evaluated whether the incidence of dissociation during weeks 1 and 4 of treatment predicted the recurrence of dissociation as a spontaneously reported adverse event in subsequent postdose monitoring sessions. Results showed similar results to the short-term study post-hoc analysis and reported that if dissociation was not reported in week 1, <10% of patients experienced that adverse event after any subsequent treatments. Compared to week 1, the occurrence in week 4 was more closely associated to later recurrence (table 50) (53).

None of the TEAEs of dissociation in the completed Phase 2 and 3 TRD studies were reported as SAEs.

Discontinuation of treatment due to dissociative/perceptual changes was only reported in isolated cases. Across all completed phase 3 studies (TRANSFORM-1/2/3 and SUSTAIN-1/2) in TRD, discontinuation of ESK-NS due to dissociation occurred in 0.4% of patients. [redacted] (46).

Table 48: Incidence and Resolution of Treatment-emergent Adverse Events of Dissociation in Completed Phase 3 TRD Studies

Study Phase	Treatment (+ Oral AD)	N	Dissociation TEAE[a]	Severe Dissociation TEAEs[a]	Discontinuatons due to Dissociation TEAEs[a]	Proportion of Dissociation TEAEs Reported on Dosing Days with Same Day Resolution[c]
TRANSFORM-1 (Fixed-Dose)						
Induction Phase	Esk 56 mg:	115	30 (26.1%)	2 (1.7%)	0	123/125 (98.4%)
	Esk 84 mg:	116	32 (27.6%)	7 (6.0%)	0	152/153 (99.3%)
	Placebo:	113	4 (3.5%)	0	0	21/21 (100%)

TRANSFORM-2 (Flex-Dose)						
Induction Phase	Esk 56-84 mg:	115	30 (26.1%)	4 (3.5%)	0	169/172 (98.3%)
	Placebo:	109	4 (3.7%)	0	0	13/13 (100%)
Pooled TRANSFORM-1/2						
Induction Phase	Total Esk[b]:	346	92 (26.6%)	13 (3.8%)	0	444/450 (98.7%)
	Total Placebo:	222	8 (3.6%)	0	0	34/34 (100%)
TRANFORM-3						
Induction Phase	Esk 28-84 mg:	72	9 (12.5%)	0	0	39/39 (100%)
	Placebo:	65	1 (1.5%)	0	0	0
SUSTAIN-1						
Induction Phase	Esk 56-84 mg:	437	82 (18.8%)	5 (1.1%)	2 (0.5%)	330/331 (99.7%)
Optimization (OP) Phase	Esk 56-84 mg:	455	73 (16.0%)	5 (1.1%)	0	321/321 (100%)
Maintenance (MA) Phase	Esk 56-84 mg:	152	35 (23.0%)	1 (0.7%)	0	178/179 (99.4%)
	Placebo:	145	0	0	0	0
SUSTAIN-2						
Induction Phase	Esk 28-84 mg:	779	182 (23.4%)	11 (1.4%)	5 (0.6%)	610/615 (99.2%)
OP/MA Phase	Esk 28-84 mg:	603	113 (18.7%)	4 (0.7%)	0	828/833 (99.4%)

[a] Note: Incidence is this column is based on the number of subjects experiencing at least one adverse event, not the number of events.

[b] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

[c] Note: Numerator is the number of dverse events occurring post-dose on a dosing day. Denominator is the total number of occurrences of a AE. A subject may be counted more than once if they had multiple occurrences of an AE.

Table 49: Incidence of Dissociation in Week 1 and Incidence/Frequency of Dissociation in Weeks 2-4 (52).

AE	4-week incidence	Week 1 incidence (number of monitoring periods [0-2] AE observed)		Number of patients with AEs in Weeks 2-4	Number of Sessions (0-6) in which an AE was experienced in Weeks 2-4
Dissociation	26.6%	None – 77.7% (n=268)	→	5.6% (n=15)	1.95
		Once – 22.3% (n=77)	→	71.4% (n=55)	4.14
		Twice – 11.3% (n=39)	→	94.9% (n=37)	4.57
Data sample was combination of date from the 3 intranasal Esketamine groups from the fixed-dose and flexible-dose studies (N=345). The first week incidence groups are not mutually exclusive – the "Twice" group is a subset of the "Once" group					

Table 50: Rates of Dissociation Recurrency According to Frequency of Dissociation Occurrence in Week 1 (53).

Postdose Monitoring Period	**No. of Patients**	**Overall Incidence (%)**	**None in Week 1 (% n/N)**	**Once in Week 1(%, n/N)**	**Twice in Week 1 (%, n/N)**

Weeks 2-4	949	15.7	5.6 (44/790)	48.2 (41/85)	86.5 (64/74)
Weeks 5-8	918	12.6	6.1 (46/759)	29.8 (25/84)	60 (45/75)
Months 3-6	595	14.4	7.6 (36/476)	26.2 (17/65)	61.1 (33/54)
Months 6-12	595	8.7	4.6 (22/476)	18.5 (12/65)	33.3 (18/54)

n/N represents the number of patients who experienced a recurrence of dissociation/number of patients who contributed data to the time period depicted in the row

Mental disturbances (anxiety, cognition and psychosis)

Psychotic-like symptoms

Symptoms of psychosis were assessed as part of the safety evaluation of ESK-NS in phase 2/3 clinical trials in patients with TRD and the long-term extension safety study SUSTAIN-3. The four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+; score range, 0-24) was used to assess for potential treatment-emergent symptoms, including suspiciousness, hallucinations, unusual thought content, and conceptual disorganization. Across all completed studies, mean BPRS+ total scores increased to maximum values of less than 1 (very mild symptoms) 40 minutes postdose from baseline and generally returned to predose values 1.5 hours postdose. In the short-term studies, the mean BPRS+ score remained below 1.2 at all postdose timepoints.

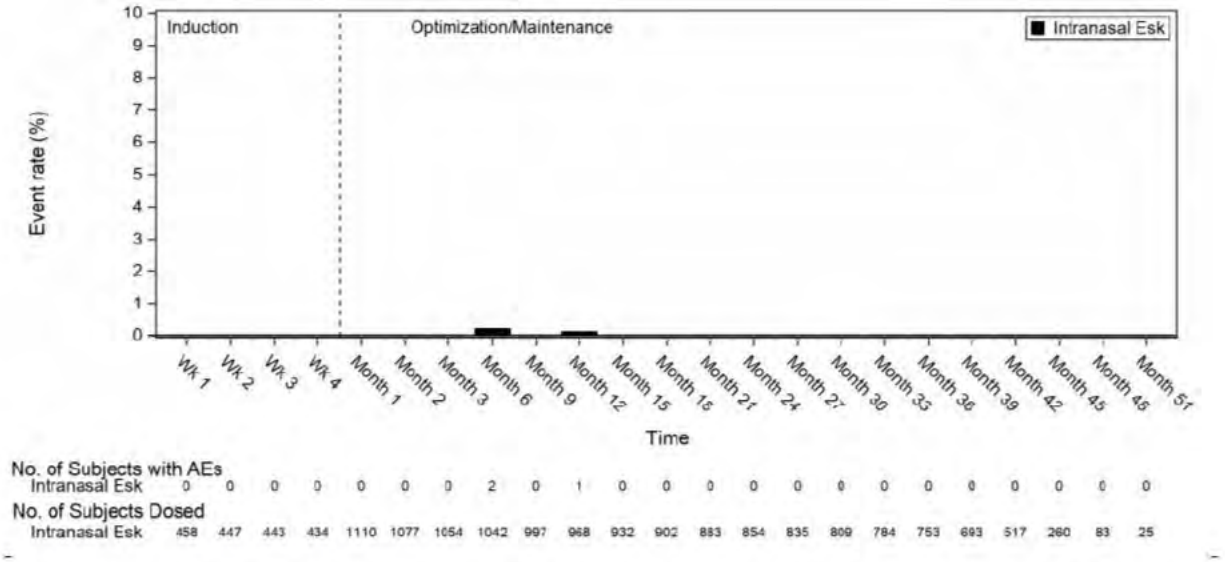
Adverse events (psychosis)

The search strategy and a list of PTs returned by the search for the important risk of psychosis are: Acute psychosis, Affective disorder, Alcoholic psychosis, Bipolar I disorder, Epileptic psychosis, Hysterical psychosis, Mania, Parkinson's disease psychosis, Postictal psychosis, Psychosis postoperative, psychotic disorder, Psychotic disorder due to a general medical condition, Reactive psychosis, Rebound psychosis, Schizoaffective disorder, Substance-induced psychotic disorder, Transient psychosis.

No adverse events (AEs) of psychosis were reported in any of the completed phase 2/3 clinical studies, Individual TEAEs of thinking abnormal and illusion were reported in isolated cases across the studies and were not severe or serious.

[redacted]

[redacted]



Note: Adverse events rate =number of subjects dosed and with TEAEs in interval / number of subjects dosed within interval.
Study week (or month) is defined using the phase study day by every 7 days (or 28 days)
The intervals with the number of patients <10 are not presented.
[GSFAE14.RTF] [JNJ-54135419\TRD3008\DBR_IA3\RE_IA3\PROD\GSFAE14.SAS] 27APR2021, 03:27

Cognition

The literature remains inconclusive regarding the effect of ketamine on cognition. A literature review summarised several studies that examined cognitive function in ketamine users. Infrequent ketamine or recreational users did not appear to be associated with long-term cognitive impairment(50). Instead, long-term cognitive deficits appeared to be confined to those who used the drug heavily (an average of 20 days per months), taking an average dose of 3.80 (± 2.36) grams per session (54). Frequent ketamine users were also impaired on cognitive testing after long-term use (12 months) (55), but the effects did not increase over time and were reversible after ketamine discontinuation.

Relatively few studies have evaluated the neurocognitive effect of ketamine administration in adults with TRD, but a recent review reported that there was no evidence for cognitive impairment following subanesthetic administration of ketamine (56). In fact, preliminary evidence suggests a putative pro-cognitive effect of ketamine on selected measures of cognition in mood disorder and TRD (57). Based on these observations impaired cognition was a TEAE of special interest assessed during the esketamine clinical trial program and included in the RMP as an important potential risk (cognitive disorders and memory impairment).

The effect of esketamine on cognitive functioning was evaluated in the clinical trials program (Table 51) using a computerized cognitive battery (Cogstate battery) and Hopkins Verbal Learning Test-Revised (HVLT-R). The Cogstate battery provided assessment of multiple cognitive domains including attention, visual learning and memory, and executive function, and the HLVT-R measured verbal learning and memory.

Results of a phase 1, double-blind, placebo-controlled, cross-over trial (TRD1005) in healthy volunteers showed that a single ESK-NS 84 mg dose produced a transient decline in cognitive function (attention, visual and working memory, reaction time, and executive functioning), an increase in mental effort required to complete the Cogstate computerized test and an increase in sleepiness at 40 minutes post-dose, which resolved by 2 hours post-dose (58).

Across the short-term phase 3 studies of ESK-NS in adults with TRD, performance on each of the cognitive tests was either improved from baseline or appeared stable relative to baseline both at the end of the DB induction phase and at the 2-week follow-up assessment. A slight slowing of reaction time (RT) on the Detection Test was observed in the elderly subjects in TRASNFORM-3 for both ESK-NS + OAD and OAD+PBO-NS groups (Cohen's d=0.12 and 0.18, respectively). This observation was considered unlikely to be of clinical relevance. The results indicated that treatment with ESK-NS + OAD for up to 4 weeks did not influence any aspect of cognition studied in adult with TRD and was not associated with any systematic changes in cognition in the elderly subjects with repeated dosing of ESK-NS(44).

Similarly, comparison of the results for the DB maintenance phase of the relapse prevention trial SUSTAIN-1 showed no evidence for deterioration of cognitive performance with repeated, longer-term intermittent ESK-NS dosing. Specifically, during the maintenance phase, performance in the ESK-NS + OAD and PBO-NS + OAD groups improved, or remained similar, to that at baseline on all cognitive tests, including tests of simple and choice RT; visual memory; verbal memory; visuospatial memory and sequencing; and working memory (44).

In the long-term safety and maintenance trial SUSTAIN-2, the performance on each of the cognitive tests relative to baseline demonstrated an improvement or remained stable in each treatment phase in the all enrolled analysis set (n=796). This pattern of performance was also evident for the subgroup of subjects <65 years of age. In elderly subjects (65 years of age and above), while performance on all 4 tests of higher cognitive functioning improved or remained stable, simple, and choice reaction time showed slowing that began at Week 20 of the OP/MA phase. While a slowing of processing speed was observed, with maximal effect at Week 44, there was no evidence of broader attention deficit. It is recognized that attention is a complex cognitive domain; broard impairments of attention are anticipated to affect performance on tests of other, more complex cognitive domains. In the current study, broader impairments in attention was not affected. Rather, the slowing observed in elderly subjects appears as an isolated observation related solely to RT, not a broad attentional impairment(44).

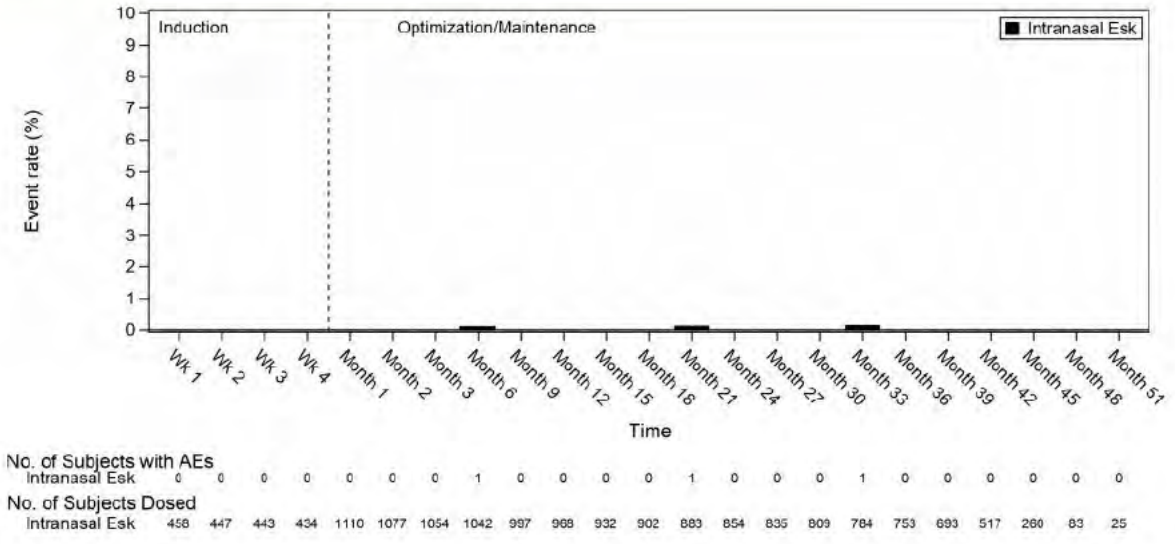
[redacted]

Adverse events: Cognition

The frequency of reported AEs related to cognitive disorders and memory impairment was 4.1 % in the All Clinical Trials Population (Completed Phase 2 and 3 trials) and 2.1 times higher in the ESK-NS + OAD group vs. the PBO + OAD group in the DB trials (3.9% vs. 1.9%) (Table 51). The OR (95% CI) of 2.1 (0.9, 5.3) indicated that there was insufficient evidence to support that the true OR of a cognitive disorders-related or memory impairment-related event was greater than 1 when comparing ESK-NS + OAD to PBO-NS + OAD. No fatal or serious events were reported in either group in the DB trials, and no fatal or serious events were reported in the All Clinical Trials Population. In the DB trials, 92.3% of the events in the ESK-NS group were mild or moderate in severity, with 2 (7.7%) of the events being severe in the ESK-NS + OAD group compared with 1 event (11.1%) in the PBO-NS + OAD group. In the All Clinical Trials Population, 97.6% of the events were mild or moderate, and 2.5% of the events were severe. In the All Clinical Trials Population, the outcome was reported as "Recovered" for 74 (92.5%) events, and "Not recovered" for 6 (7.5%) events. Of the 6 events with an outcome of "Not recovered", only 2 events (amnesia and memory impairment) occurred in the ESK-NS + OAD group; follow-up information from the investigational sites received after the data-lock point confirmed an outcome of "Recovered" for these 2 events.

No TEAEs corresponding to the PT Cognitive disorder or the PT Cognitive motor disorder were reported in the Phase 3 trials in TRD.

[redacted]



Note: Adverse events rate =number of subjects dosed and with TEAEs in interval / number of subjects dosed within interval.
Study week (or month) is defined using the phase study day by every 7 days (or 28 days)
The intervals with the number of patients <10 are not presented.

Given the recommended intermittent dosing frequency for ESK-NS and considering that most events related to cognitive disorders and memory impairment following long-term use in clinical trials were neither severe nor serious, were generally self-limiting, and resolved without intervention, the impact on the risk-benefit balance of the product is expected to be low.

Table 51 :Frequency (95% CI), Seriousness, Outcomes, and Severity of Cognitive Disorders and Memory Impairment-related Events in Clinical Trials (TRD)

	All Randomised, Blinded Trials Population		**All Clinical Trials Population**
	Esketamine + Oral AD	**Placebo + Oral AD**	**Esketamine + Oral AD**
	(N=571)	**(N=486)**	**(N=1,708)**
Frequency	**n (%)**	**n (%)**	**n (%)**
Subjects With Cognitive Disorders and Memory Impairment-related Events[a]	**22 (3.9%)**	**9 (1.9%)**	**70 (4.1%)**
Odds ratio	2.1	-	-
95% CI[b]	0.9 to 5.3	-	-
Seriousness/Outcomes of Events[c]	**26**	**9**	**80**
Fatal	0	0	0
Serious	0	0	0
Recovered	24 (92.3%)	5 (55.6%)	74 (92.5%)
Recovered with sequelae	0	0	0
Recovering	0	0	0
Not recovered	2 (7.7%)	4 (44.4%)	6 (7.5%)
Unknown	0	0	0
Missing	0	0	0
Severity of Events[c]			
Mild	12 (46.2%)	5 (55.6%)	41 (51.3%)
Moderate	12 (46.2%)	3 (33.3%)	37 (46.3%)
Severe	2 (7.7%)	1 (11.1%)	2 (2.5%)
Missing	0	0	0

Note: MedDRA versions 18.0 (SYNAPSE) and 20.0 (TRANSFORM-1, TRANSFORM-2, SUSTAIN-1, SUSTAIN-2, and TRANSFORM-3) were used to classify the adverse event information that is summarised in this table.

The following trials are included in the All Randomised, Blinded Trials Population: TRANFORM-1 (Double-blind Phase), TRANFORM-2 (Double-blind Phase), SUSTAIN-1 (Double-blind Maintenance Phase), TRANFORM-3 (Double-blind Phase), and SYNAPSE (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: TRANFORM-1, TRANFORM-2, SUSTAIN-1, SUSTAIN-2, TRANFORM-3, and SYNAPSE (excluding Double-blind Phase esketamine 14 mg).

Subjects in the All Randomised, Blinded Trials Population who were exposed to esketamine in trials TRANFORM-1 or TRANFORM-2 and transferred to SUSTAIN-1 and were re-randomised to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomised, Blinded Trials Population who received both esketamine and placebo in SYNAPSE in the Double-blind Phase were counted in both treatment groups.

Key: AD=Antidepressant; CI=Confidence Interval; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Adverse Event; N=Number; TRD=Treatment-resistant Depression.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'Cognitive Disorders and Memory Impairment-related Events'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomised, Blinded Trials Population.

	All Randomised, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD	Placebo + Oral AD	Esketamine + Oral AD
	(N=571)	(N=486)	(N=1,708)
c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'Cognitive Disorders and Memory Impairment-related Events' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarised.			

Anxiety

Although anxiety and depression are considered 2 separate classes of disorders, they often occur comorbidly with many overlapping symptoms (59). During the clinical trial program for esketamine in TRD certain psychiatric comorbidities were excluded. However, the most common psychiatric comorbidities, i.e. comorbid anxiety disorder was not an exclusion criteria. The Mini-International Neuropsychiatric Interview (MINI) was used to identify the presence of comorbid psychiatric conditions during fist screening visit to confirm patient eligibility. The pooled incidence of common psychiatric comorbidities upon enrollment in the phase 3 TRD trials in adults 18-64 (TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1) and separately in adults ≥ 65 (TRANSFORM-3) can be found in the table 52 below (60).

Table 52 MINI Results – Pooled (TRANSFORM-1, TRANSFORM-2, SUSTAIN-1) and TRANSFORM-3 (60).

	Pooled Incidence ESK patients (N=773)	TRANSFORM-3 Esk patients (N=72)
Generalized Anxiety Disorder	9.2% (n=71)	13.9% (n=10)
Panic Disorder	5.4% (n=42)	5.6% (n=4)
Social Anxiety Disorder	4.7% (n=36)	5.6% (n=4)
Agoraphobia	4.5% (n=35)	2.8% (n=2)
Posttraumatic Stress Disorder	1.6% (n=12)	0

In 2 short-term (TRANSFORM-1/2) and 2 long-term (SUSTAIN-1/2) phase 3 studies in patients with TRD, a high percentage of ESK-NS treated subjects (62% to 80%) had moderate to severe levels of anxiety symptoms at baseline using self-reported Generalized Anxiety Disorder 7-item Scale (GAD-7) scores. Further, a post hoc pooled analysis of TRANSFORM-1 and 2 showed that 22.3% (126/564), 14.2% (80/565), and 72.9% (412/565) of patients had anxious depression, comorbid anxiety disorder, or anxious distress, respectively, at baseline. Reflecting numbers reported in other studies in this patient population. (61)

The incidence of anxiety was reported in the clinical trial program of esketamine as TEAEs of special interest.

Adverse events - anxiety

The search for TEAEs in the category of anxiety included the following PTs: *Anxiety, Anticipatory Anxiety, and Anxiety Disorder.* The overall incidences of these TEAEs in the Phase 3 TRD studies are summarized in table 53.

TEAE grouped terms related to anxiety were reported at higher rates in the ESK-NS + OAD groups than in the OAD + PBO-NS group in the controlled Phase 3 studies/study phases in adults (TRANSFORM-1/2: 9.0% vs 5.4%, respectively; DB MA phase of SUSTAIN-1: 7.9% vs 3.4%), but was reported less often in the ESK-NS + OAD group for elderly subjects in TRANSFORM-3 (2.8% vs 7.7%) (Table 53). There was no apparent increase in the overall incidence of anxiety TEAEs with longer-term ESK-NS treatment, with anxiety preferred terms reported in 6.5% of ESK-NS treated subjects during the IND phase and 4.3% during the OP/MA phase of the SUSTAIN-2 study. In the phase 2 study SYNAPSE, across both panels, TEAEs in the category of anxiety were only reported in Panel B for 2 subjects: 1 subject in PBO-NS/ESK-NS 56-mg group had a TEAE of anxiety during the DB phase and 1 subject in PBO-NS/ESK-NS/open-label ESK-NS group had a TEAE of anxiety during the OL phase. Anxiety (grouped term) is identified as an ADR for ESK-NS (44, 62)[redacted]

In the completed Phase 3 studies in TRD, TEAEs related to anxiety were primarily mild or moderate in severity, transient and self-limited. Severe anxiety TEAEs (individual PT) were uncommon an occurred at incidence rates of 0.3% to 1.4% across studies/study phases in the ESK-NS + OAD treatment groups (62). In the pooled short-term studies TRANSFORM-1/2 severe anxiety TEAEs were reported in 3 subjects (0.9%) in the total ESK-NS + OAD group vs 1 subject (0.5%) in OAD + PBO-NS. In the elderly study TRANSFORM-3, no cases were reported in the ESK-NS +OAD group vs 1 case (1.5%) in the OAD + PBO-NS group. Severe TEAEs of anxiety occurred in the IND phase (2 subjects [0.5%]) and in the MA phase (2 subjects [1.3%] in ESK-NS + OAD and no cases in the OAD + PBO-NS group) and OP/MA phase (2 subjects [0.3%] of the long-term safety study SUSTAIN-2) (44). [redacted]

Across all studies/study phases, the vast majority of TEAEs of anxiety, agitation, anxiety disorder, or anticipatory anxiety required no rescue medication. Less than 4% of esketamine-treated subjects were treated with rescue medication for these events. The most frequently used rescue medication was short-acting benzodiazepine lorazepam, administered at rates up to 1.7% of esketamine-treated subjects across studies/study phases (44).

The rates of TEAEs based on the PT of anxiety over the course of the studies generally decreased after the first week of dosing in the pooled short-term studies TRANSFORM-1/2, and in the IND phase of the long-term studies (44).

Most of the TEAEs of anxiety (PT) occurred on the day of dosing and resolved spontaneously the same day (see Table 53) In the pooled short-term studies (TRANSFORM-1/2), 69.2% of the TEAEs of anxiety reported in the ESK-NS + OAD group occurred on the day of dosing (compared with 53.3% in the OAD + PBO-NS group); of these TEAEs, 86.1% resolved the same day (vs. 37.5% in the OAD + PBO-NS group). Both the rate of occurrence of the TEAEs of anxiety on the day of dosing and rate of same-day resolution were higher in the ESK-NS + OAD group, compared with the OAD + PBO-NS group in all controlled studies. In the MA phase of the relapse prevention study, approximately half (47.1%) the TEAEs of anxiety reported in the ESK-NS + OAD group occurred on the day of dosing (compared with 33.3% in the OAD + PBO-NS group), with 62.5% of these TEAEs resolving the same day (compared with 0% in the OAD + PBO-NS group). In the long-term OL study, 57% of the TEAEs of anxiety reported across all study phases were observed on the day of dosing, and 60.3% of these TEAEs resolved the same day (Table 53) (44). [redacted]

Table 53: Overall Incidence of Treatment-emergent Adverse Events in the Category of Anxiety and Resolution of Adverse Events of Anxiety in Completed Phase 3 TRD Studies (44)

			Category of Anxiety	Anxiety (Individual PT)		
Study Phase	Treatment (+ Oral AD)	N	Subjects with any TEAE in the Category of Anxiety[a]	Subjects with TEAE of Anxiety (individual PT)[a]	Proportion of TEAEs occurring on dosing days[b]	Proportion of TEAEs occurring on dosing days with same day resolution
TRANSFORM-1 (Fixed-Dose)						
Induction Phase	Esk 56 mg:	115	10 (8.7%)	10 (8.7%)	8/14 (57.1%)	8/8 (100%)
	Esk 84 mg:	116	9 (7.8%)	9 (7.8%)	15/20 (75%)	12/15 (80%)
	Placebo:	113	7 (6.2%)	7 (6.2%)	5/10 (50%)	2/5 (40%)
TRANSFOMR-2 (Flex-Dose)						
Induction Phase	Esk 56-84 mg:	115	12 (10.4%)	12 (10.4%)	13/18 (72.2%)	11/13 (84.6%)

	Placebo:	109	5 (4.6%)	5 (4.6%)	3/5 (60%)	1/3 (33.3%)
Pooled TRANSFORM-1/2						
Induction Phase	Total Esk[c]:	346	31 (9.0%)	31 (9.0%)	36/52 (69.2%)	31/36 (86.1%)
	Total Placebo:	222	12 (5.4%)	12 (5.4%)	8/15 (53.3%)	3/8 (37.5%)
TRANSFORM-3						
Induction Phase	Esk 28-84 mg:	72	3 (4.2%)	2 (2.8%)	2/2 (100%)	2/2 (100%)
	Placebo:	65	5 (7.7%)	5 (7.7%)	6/9 (66.7%)	5/6 (83.3%)
SUSTAIN-1						
Induction Phase	Esk 56-84 mg:	437	32 (7.3%)	31 (7.1%)	28/40 (70%)	22/28 (78.6%)
Optimization Phase	Esk 56-84 mg:	455	11 (2.4%)	11 (2.4%)	8/19 (42.1%)	7/8 (87.5%)
Maintenance Phase	Esk 56-84 mg:	152	12 (7.9%)	12 (7.9%)	8/17 (47.1%)	5/8 (62.5%)
	Placebo:	145	5 (3.4%)	5 (3.4%)	2/6 (33.3%)	0/2 (0%)
SUSTAIN-2						
Induction Phase	Esk 28-84 mg:	779	51 (6.5%)	51 (6.5%)	38/68 (55.9%)	18/38 (47.4%)
OP/MA Phase	Esk 28-84 mg:	603	26 (4.3%)	26 (4.3%)	35/60 (58.3%)	26/35 (74.3%)
IND and OP/MA Phases	Esk 28-84 mg:	802	72 (9.0%)	72 (9.0%)	73/128 (57.0%)	44/73 (60.3%)

Study Phase	Treatment (+ Oral AD)	N	Category of Anxiety: Subjects with any TEAE in the Category of Anxiety[a]	Anxiety (Individual PT): Subjects with TEAE of Anxiety (individual PT)[a]	Anxiety (Individual PT): Proportion of TEAEs occurring on dosing days[b]	Anxiety (Individual PT): Proportion of TEAEs occurring on dosing days with same day resolution
TRANSFORM-1 (Fixed-Dose)						
Induction Phase	Esk 56 mg:	115	10 (8.7%)	10 (8.7%)	8/14 (57.1%)	8/8 (100%)
	Esk 84 mg:	116	9 (7.8%)	9 (7.8%)	15/20 (75%)	12/15 (80%)
	Placebo:	113	7 (6.2%)	7 (6.2%)	5/10 (50%)	2/5 (40%)
TRANSFORM-2 (Flex-Dose)						
Induction Phase	Esk 56-84 mg:	115	12 (10.4%)	12 (10.4%)	13/18 (72.2%)	11/13 (84.6%)
	Placebo:	109	5 (4.6%)	5 (4.6%)	3/5 (60%)	1/3 (33.3%)
Pooled TRANSFORM-1/2						
Induction Phase	Total Esk[c]:	346	31 (9.0%)	31 (9.0%)	36/52 (69.2%)	31/36 (86.1%)
	Total Placebo:	222	12 (5.4%)	12 (5.4%)	8/15 (53.3%)	3/8 (37.5%)
TRANSFORM-3						
Induction Phase	Esk 28-84 mg:	72	3 (4.2%)	2 (2.8%)	2/2 (100%)	2/2 (100%)
	Placebo:	65	5 (7.7%)	5 (7.7%)	6/9 (66.7%)	5/6 (83.3%)
SUSTAIN-1						
Induction Phase	Esk 56-84 mg:	437	32 (7.3%)	31 (7.1%)	28/40 (70%)	22/28 (78.6%)
Optimization Phase	Esk 56-84 mg:	455	11 (2.4%)	11 (2.4%)	8/19 (42.1%)	7/8 (87.5%)
Maintenance Phase	Esk 56-84 mg:	152	12 (7.9%)	12 (7.9%)	8/17 (47.1%)	5/8 (62.5%)
	Placebo:	145	5 (3.4%)	5 (3.4%)	2/6 (33.3%)	0/2 (0%)

SUSTAIN-2						
Induction Phase	Esk 28-84 mg:	779	51 (6.5%)	51 (6.5%)	38/68 (55.9%)	18/38 (47.4%)
OP/MA Phase	Esk 28-84 mg:	603	26 (4.3%)	26 (4.3%)	35/60 (58.3%)	26/35 (74.3%)
IND and OP/MA Phases	Esk 28-84 mg:	802	72 (9.0%)	72 (9.0%)	73/128 (57.0%)	44/73 (60.3%)

Note: TEAEs in the category of anxiety included *Anxiety, Anticipatory Anxiety, and Anxiety Disorder.*

[a] Note: incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

[b] Note: Numerator is the number of adverse events occurring post-dose on a dosing day. Denominator is the total number of occurrences of a AE. A subject may be counted more than once if they had multiple occurrences of an AE.

[c] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

Isolated cases of anxiety (individual PT) were reported as serious. Most of these events were considered by the investigator to be either not related or of doubtful relationship to esketamine. SAEs of anxiety and delusion considered possibly related to esketamine by the investigator were reported in a subject in SUSTAIN-2, who had a history of MDD and generalized anxiety disorder, as well as having a retrospectively reported ongoing history of alcohol abuse. These TEAEs were reported together with the SAE of alcohol abuse on Day 5 and resulted in withdrawal from the study. In the short-term elderly study, 1 subject in the ESK-NS + OAD group (Subject in TRANSFORM-3) had a SAE of anxiety disorder on Day 20 of the IND phase, which was considered by the investigator to be possibly related to ESK-NS and possibly related to OAD treatment; the TEAE occurred 4 days after intranasal dosing and during the hospitalization of the patient's spouse. The Sponsor considers that this event was not related to ESK-NS or OAD given the timing of the event and the subject's personal circumstances (44). [redacted]

[redacted]

Based on clinical review it was considered that TEAEs of agitation (including psychomotor agitation), as well as restlessness, tremor, and fear were also among reported clinical presentations of anxiety. These symptoms had a transient character and were rarely severe or serious.

Extreme levels of anxiety (TEAEs of panic attacks) were reported at low rates (below 2% across phase 2 and 3 studies/study phases and [redacted] and led to treatment discontinuation in 3 subjects across the completed Phase 3 studies (44, 46).

Hypertension

Transient cardiovascular stimulatory effects have been reported with ketamine, beginning shortly after dosing for general anesthesia and in patients with MDD (63). Thus, cardiovascular risk is an important identified risk for esketamine in the risk management plan (RMP) that are well-characterized and mitigated through comprehensive risk minimization and pharmacovigilance activities.

Across the completed phase 2 and 3 trials the impact of esketamine on BP and heart rate was evaluated in a large cohort (N=1708) of patients with TRD who had no clinically important cardiovascular disease or had hypertension controlled by antihypertensive medications (62).

Transient, primarily asymptomatic, increases in systolic and diastolic BP were observed following esketamine administration in the Phase 2 and 3 studies in TRD, with maximum mean changes typically observed within 40 minutes of dosing and mean BP values subsequently returning to, or close to, pre-dose values within the 1.5-hour post-dose time-point (62). BP elevation were in general not associated with symptoms, rarely required treatment with antihypertensive medication, and did not result in serious cardiovascular safety sequalae (63). In the TRD clinical studies, unless clinically indicated, it was recommended that transient increases in BP not be treated, as the BP typically returns to predose values within 2 hours as described following esk-ns administration.

Based on 3 short-term studies TRANSFORM-1/2/3 in TRD, the mean PBO-adjusted increases in SBP and DBP over time were about 7 to 9 mm Hg in SBP and 4 to 6 mm Hg in DBP at 40 minutes post-dose and 2 to 5 mm Hg in SBP and 1 to 3 mm Hg in DBP at 1.5 hours post-dose in patients receiving ESK-NS. In the fixed dose study TRANFORM-1, differences between the maximum mean changes in BP between the 56 mg and 84 mg doses of esketamine were small and not suggestive of a dose response (14.3 and 15.0 mm Hg, respectively for SBP; 8.9 and 9.4 mm Hg, respectively for diastolic BP). Elevations in blood pressure can be higher or longer in individual patients (44, 64).

In a post hoc analysis of pooled data from two long-term studies SUSTAIN-1 and SUSTAIN-2 the incidence of increased BP during weeks 1 and 4 of treatment was evaluated to predict the recurrence of increased BP as a spontaneously reported AE in subsequent postdose monitoring sessions. Results showed that if BP increase was not reported in week 1, ≤4% of patients experienced that AE during all subsequent postdose monitoring periods. Compared to week 1, the occurrence in week 4 was more closely associated to later recurrence (Table 54) (53, 64).

Table 54 : Rates of Increased Blood Pressure Recurrence According to Frequency of Increased Blood Pressure Occurrence in Week 1 (53, 64).

Postdose Monitoring Period	No. Of Patients	Overall Incidence (%)	None in Week 1 (%, n/N)	Once in Week 1 (%, n/N)	Twice in Week 1 (%, n/N)
Weeks 2-4	949	5.1	2.3 (21/908)	56.5 (13/23)	77.8 (14/18)
Weeks 5-8	918	3.9	1.9 (17/878)	40.9 (9/22)	55.6 (10/18)
Month 3-6	595	4.2	3.0 (17/574)	36.4 (4/11)	40.0 (4/10)
Months 6-12	595	2.2	1.7 (10/574)	9.1 (1/11)	20.0 (2/10)

n/N represents the number of patients who experienced a recurrence of increased blood pressure/number of patients who contributed data to the time period depicted in the two

In the short-term studies TRANSFORM-1/2, increases in blood pressure were unrelated to the pretreatment BP.

The most common blood pressure abnormality reported during the Phase 3 studies was an abnormal (transient) increase in DBP, which was reported in 5% to 10% of subjects in the ESK-NS + OAD treatment group across studies/treatment phases. The rate of abnormal DBP increases was higher for the ESK-NS + OAD group than the OAD + PBO-NS group in the pooled short-term DB studies in adults (TRANSFORM-1/TRANSFORM-2: 8.1% vs. 1.8%) but this difference was not observed in the short-term study in elderly subjects (TRANSFORM-3) (1.4% vs. 1.5%). During the long-term studies (SUSTAIN-1 and SUSTAIN-2), blood pressure abnormalities were reported at similar rates across the study phases. In SUSTAIN-1, the rate of abnormal DBP increases was higher for the ESK-NS + OAD group than for the OAD + PBO-NS group during the DB MA phase (7.9% vs. 1.4%). Abnormal increases in SBP were reported at low rates (0.9% to 2.8% of subjects in the ESK-NS + OAD group across studies/treatment phases) (table 55) (44).

The proportion of subjects with markedly abnormal elevations of SBP to elevation ≥ 180 mm Hg or DBP to ≥110 mm Hg (acute hypertension) were reported at rates of <5% among ESK-NS treatment groups for the pooled studies TRANSFORM-1/2 (0.9% for total OAD+PBO-NS) and all study phases of SUSTAIN-1 and SUSTAIN-2; the exception was for the study TRANFORM-3 in elderly subjects where the percentage was 11.1% (6.2% of OAD + PBO-NS) (Table 55). These elevations occurred primarily within 1.5 hours after dosing and the rates of subjects meeting these acute hypertension criteria were higher in subjects with a history of hypertension than those without (pooled TRANSFORM-1/2 studies: 7.6% vs. 4.3%; long-term safety study SUSTAIN-2: 7.3% vs 2.9%; relapse-prevention study SUSTAIN-1 [any phase]: 5.5% vs. 4.1%). These increases occurred at a higher rate in elderly subjects vs. younger adults: 11.1% vs. 4.9% in the short-term studies (44).

In the Phase 2 study SYNAPSE (Panel A and Panel B combined), increased SBP (≥20 mm Hg to a value of ≥180 mm Hg) was observed in 2 subjects (both treated with esketamine 84 mg), and increased DBP (≥15 mm Hg to a value of ≥105 mm Hg) in 6 subjects (2 subjects treated with placebo and 4 subjects treated with esketamine) in Period 1. In Period 2, increased SBP was observed in 2 subjects, and increased DB was reported in 3 subjects (all in the esketamine treatment groups) (44).

Table 55: Incidence of Treatment-emergent Abnormal Blood Pressure Values Relative to Baseline at Any Time in Completed Phase 3 TRD Studies (44).

			SBP (mm Hg)		DBP (mm Hg)		
Study Phase	Treatment (+Oral AD)	N	Decrease ≥20 and value ≤90	Increase ≥20 and value ≥180	Decrease ≥15 and value ≤50	Increase ≥15 and value ≥105	Acute Hypertension[b]
TRANSFORM-1 (Fixed-Dose)							
Induction Phase	Esk 56 mg:	115	3 (2.6%)	6 (5.2%)	2 (1.7%)	8 (7.0%)	8 (7.0%)

	Esk 84 mg:	116	3 (2.6%)	2 (1.7%)	6 (5.2%)	10 (8.6%)	5 (4.3%)
	Placebo:	113	3 (2.7%)	0	0	4 (3.5%)	2 (1.8%)
TRANSFORM-2 (Flex-Dose)							
Induction Phase	Esk 56-84 mg:	115	1 (0.9%)	1 (0.9%)	0	10 (8.7%)	4 (3.5%)
	Placebo:	109	3 (2.8%)	0	3 (2.8%)	0	0
Pooled TRANSFORM-1/2							
Induction Phase	Total Esk[a]:	346	7 (2.0%)	9 (2.6%)	8 (2.3%)	28 (8.1%)	17 (4.9%)
	Total Placebo:	222	6 (2.7%)	0	3 (1.4%)	4 (1.8%)	2 (0.9%)
TRANSFORM-3							
Induction Phase	Esk 28-84 mg:	72	1 (1.4%)	2 (2.8%)	0	1 (1.4%)	8 (11.1%)
	Placebo:	65	6 (9.2%)	1 (1.5%)	4 (6.2%)	1 (1.5%)	4 (6.2%)
SUSTAIN-1							
Induction Phase	Esk 56-84 mg:	437	20 (4.6%)	4 (0.9%)	6 (1.4%)	43 (9.8%)	15 (3.4%)
Optimization (OP) Phase	Esk 56-84 mg:	455	14 (3.1%)	4 (0.9%)	6 (1.3%)	29 (6.4%)	12 (2.6%)
Maintenance (MA) Phase	Esk 56-84 mg:	152	5 (3.3%)	1 (0.7%)	3 (2.0%)	12 (7.9%)	3 (2.0%)
	Placebo:	145	7 (4.8%)	0	1 (0.7%)	2 (1.4%)	0

SUSTAIN-2							
Induction Phase	Esk 28-84 mg:	779	25 (3.2%)	10 (1.3%)	13 (1.7%)	39 (5.0%)	18 (2.3%)
OP/MA Phase	Esk 28-84 mg:	603	37 (6.1%)	10 (1.7%)	24 (4.0%)	35 (5.8%)	18 (3.0%)
IND and OP/MA Phases	Esk 28-84 mg:	802	55 (6.9%)	18 (2.2%)	33 (4.1%)	66 (8.2%)	33 (4.1%)

Note: Percentages calculated with the number of subjects per parameter as denominator. Note: If baseline value is missing, treatment-emergent abnormal vital signs will be evaluated based on the visit value only.

[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

[b] Subjects with treatment-emergent acute hypertension have either systolic BP >=180 mm Hg (and baseline < 180 mm Hg or missing) or diastolic BP >=110 mm Hg (and baseline <110 mm Hg or missing).

Observed mean increases in pulse rate following esketamine administration were not clinically meaningful in any of the Phase 3 studies. In the controlled Phase 3 studies/study phases, the proportion of subjects with a treatment-emergent abnormal decrease or increase in pulse rate relative to baseline (≥15 bpm relative to baseline to a value ≥100 bpm) was less than 9% and similar for the ESK-NS + OAD and OAD + PBO-NS groups. In the phase 2 study SYNAPSE, abnormal increases in pulse rate were observed in no more than 2 subjects in any treatment sequence and period. No treatment-emergent events of increased HR were reported (Table 56) (44).

Table 56: Incidence of Treatment-emergent Abnormal Pulse Rate Values Relative to Baseline at Any Time in Completed Phase 3 TRD Studies (44).

			Pulse Rate (beats/min)	
Study Phase	Treatment (+Oral AD)	N	Decrease ≥ 15 and value ≤ 50	Increase ≥ 15 and value ≥ 100
TRANFORM-1 (Fixed-Dose)				
Induction Phase	Esk 56 mg:	115	3 (2.6%)	10 (8.7%)
	Esk 84 mg:	116	3 (2.6%)	9 (7.8%)
	Placebo:	113	5 (4.4%)	9 (8.0%)
TRANSFOMR-2 (Flex-Dose)				

Induction Phase	Esk 56-84 mg:	115	2 (1.7%)	6 (5.2%)
	Placebo:	109	3 (2.8%)	5 (4.6%)
Pooled TRANSFORM-1/2				
Induction Phase	Total Esk[a]:	346	8 (2.3%)	25 (7.2%)
	Total Placebo:	222	8 (3.6%)	14 (6.3%)
TRANFORM-3				
Induction Phase	Esk 28-84 mg:	72	2 (2.8%)	2 (2.8%)
	Placebo:	65	2 (3.1%)	2 (3.1%)
SUSTAIN-1				
Induction Phase	Esk 56-84 mg:	437	5 (1.1%)	28 (6.4%)
Optimization (OP) Phase	Esk 56-84 mg:	455	10 (2.2%)	33 (7.3%)
Maintenance (MA) Phase	Esk 56-84 mg:	152	6 (3.9%)	6 (3.9%)
	Placebo:	145	2 (1.4%)	5 (3.4%)
SUSTAIN-2				
Induction Phase	Esk 28-84 mg:	779	13 (1.7%)	29 (3.7%)
OP/MA Phase	Esk 28-84 mg:	603	25 (4.1%)	46 (7.6%)
IND and OP/MA Phases	Esk 28-84 mg:	802	31 (3.9%)	66 (8.2%)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: If baseline value is missing, treatment-emergent abnormal vital signs will be evaluated based on the visit value only.
[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

Adverse events (Blood pressure, Pulse rate)

The following terms were defined as criteria of significant abnormalities for pulse rate and BP in the phase 2 and 3 clinical trials:

- Abnormal High Pulse Rate: An increase from baseline of ≥15 bpm to a value ≥100 bpm
- Abnormal High SBP: an increase from baseline of ≥20 mm Hg to a value ≥180 mm Hg
- Abnormal High DBP: an increase from baseline of ≥15 mm Hg to a value of ≥105 mm Hg
- Marked BP Elevation (defined as "acute hypertension"): either SBP ≥180 mm Hg (and baseline <180 mm Hg or missing) or DBP ≥110 mm Hg (and baseline <110 mm Hg or missing).

Adverse events of interest in this category included PTs of increased BP (blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased and vascular disorders of treatment-emergent blood pressure elevation [hypertension and hypertensive crisis] and increased heart rate (heart rate increased, tachycardia) (44)

Across all completed Phase 2 and 3 studies, TEAEs of increased BP in ESK-NS treated subjects were reported at the rates ranging from 6.6% to 13.9% across studies/study phased (All clinical trial TRD population): 12.8%; All randomized, blinded trials TRD population: ESK-NS + OAD 11.6% vs OAD + PBO-NS 3.9%; OR 3.2 [1.9-5.8]), while TEAEs of increased HR occurred at lower incidences (all rates below 1.6%) (Table 57) (44).

Increased BP were reported at higher frequencies following treatment with ESK-NS + OAD compared to OAD +PBO-NS in the controlled Phase 3 studies/study phases (pooled TRANSFORM-1/2 studies: 10.1% vs 2.7% respectively; TRANSFORM-3: 13.9% vs 6.2%: SUSTAIN-1: DB MA phase of SUSTAIN-1: 8.6% vs 3.4%). Across the OL long-term safety study SUSTAIN-2, TEAEs related to increased BP were reported for 12.8% of subjects receiving ESK-NS + OAD (9.1% and 10.4% in the IND and OP/MA phases, respectively), [redacted] In the DB phases of Phase 2 study SYNAPSE, the reporting rate for TEAEs related to increased BP was 13.1% across all ESK-NS groups and 7.4% for the PBO-ns group; no TEAEs related to increased heart rate were reported in the DB phases of this study (Table 57) (44).

Most TEAEs of BP increased (≥95%) were reported on the day of dosing for ESK-NS treated subjects in the pooled short-term studies TRANSFORM-1/2 in adults and the short-term study in the elderly, and >93% of those TEAEs resolved the same day. Similarly, for each phase of the relapse prevention study SUSTAIN-1 and of long-term study SUSTAIN-2, 90% or more of all reported TEAEs of BP increased occurred on the day of dosing and 94% or more of these resolved spontaneously the same day (44). [redacted]

TEAEs of abnormal HR (extrasystoles, heart rate increased, palpitations, sinus tachycardia and tachycardia) occurred at lower incidence and were reported in 3.0% of ESK-NS treated patients in the all clinical trial TRD population (in All randomized, blinded trials TRD population: 1.6% vs. 0.8% in ESK-NS + OAD and OAD + PBO-NS, respectively; OR: 1.9 [0.5, 8.6]), of which ~97% of cardiovascular events were mild or moderate. Approximately 88% of the events resolved/were resolving(44). [redacted]

The TEAEs of increased BP or increased HR (individual PTs) in all studies were primarily mild or moderate in severity. There were no severe events of tachycardia in Phase 2 or 3 studies expect for 1 severe event each of sinus tachycardia and hypertensive crisis, both reported as SAEs in 1 subject in TRANSFORM-3 (44). [redacted]

There were no severe TEAEs of BP increased (individual PTs) reported in the pooled short-term studies TRANSFORM-1/2. In TRANSFORM-3, 1 (1.4%) subject in the ESK-NS + OAD group had a severe TEAE of BP increased. In the relapse prevention study SUSTAIN-1, a severe TEAE of BP increased was reported for 1

(0.2%) ESK-NS treated subject in the IND phase; no other severe events in this category were reported in the OP or MA phases. In the long-term safety study SUSTAIN-2, no subjects in the IND phase and 1 (0.2%) subject in the OP/MA phase reported a severe TEAE of BP increased (44).

Discontinuation of esketamine treatment due to increased BP and tachycardia occurred at rates below <2% across all completed studies in TRD (44).

Overall, due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact on the risk-benefit balance of the product is considered low; however, the impact on an individual patient may be significant. The SmPC and PL, as well as the RMP, provide information to the prescriber and the patient on how to manage the risk (62). More specifically, ESK-NS is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, and history of intracerebral hemorrhage). Prior to dosing with ESK-NS blood pressure should be assessed. After dosing with ESK-NS, blood pressure should be re-assessed at approximately 40 minutes and subsequently as clinically warranted (65).

Table 57: Overall Incidence of Treatment-emergent Adverse Events in the Categories of Increased Blood Pressure and Increased Heart Rate in Completed Phase 3 TRD studies (44).

Study Phase	Treatment (+ Oral AD)	N	Increased Blood Pressure	Increased Heart Rate
TRANSFORM-1 (Fixed-Dose)				
Induction Phase	Esk 56 mg:	115	9 (7.8%)	2 (1.7%)
	Esk 84 mg:	116	14 (12.1%)	3 (2.6%)
	Placebo:	113	5 (4.4%)	1 (0.9%)
TRANSFORM-2 (Flex-Dose)				
Induction Phase	Esk 56-84 mg:	115	12 (10.4%)	0
	Placebo:	109	1 (0.9%)	0
Pooled TRANFORM-1/TRANFORM-2				
Induction Phase	Total Esk[a]:	346	35 (10.1%)	5 (1.4%)
	Total Placebo:	222	6 (2.7%)	1 (0.5%)
TRANFORM-3				
Induction Phase	Esk 28-84 mg:	72	10 (13.9%)	0
	Placebo:	65	4 (6.2%)	0

SUSTAIN-1				
Induction Phase	Esk 56-84 mg:	437	40 (9.2%)	2 (0.5%)
Optimization (OP) Phase	Esk 56-84 mg:	455	30 (6.6%)	3 (0.7%)
Maintenance (MA) Phase	Esk 56-84 mg:	152	13 (8.6%)	0
	Placebo:	145	5 (3.4%)	0
SUSTAIN-2				
Induction Phase	Esk 28-84 mg:	779	71 (9.1%)	6 (0.8%)
OP/MA Phase	Esk 28-84 mg:	603	63 (10.4%)	9 (1.5%)
IND and OP/MA Phases	Esk 28-84 mg:	802	103 (12.8%)	14 (1.7%)

TEAEs in the category of Increased Blood Pressure included *blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, hypertension and hypertensive crisis.*

TEAEs in the category of Increased Heart Rate included: *heart rate increased, tachycardia*

Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
[a] Total esketamine row includes both the fixed-dose and flexible dose esketamine groups.

Interstitial cystitis

Interstitial cystitis and lower urinary tract symptoms have been reported in chronic ketamine abusers who tend to use a much higher dose and frequency (average of 2.77 g/day for an average of 20 days/months) than is used for depression (0.5-1.0 mg/kg infused over 40 min every 1-4 weeks) (66). In addition, chronic ketamine abusers often use multiple substances besides ketamine such as amphetamine, cocaine, and alcohol (67), which makes it unclear how much of the urological symptoms can be attributed to ketamine (68). In a comprehensive literature review the reported chronic physical effects of high-dose, near-daily, long-term ketamine use included ulcerative interstitial cystitis characterized by chronic inflammation and urothelial ulceration. Cessation of ketamine provide some relief of symptoms. The prevalence is difficult to determine, as it is seen in recreational users who often do not seek help. The majority of cases resolve after stopping ketamine use, one-third remaining static (50, 67, 69). Data from *In vitro* studies suggest that ketamine-induced urological toxicity (KIUT) to urothelial cells is associated with prolonged elevation of cytosolic calcium concentration triggered by ketamine urinary concentration >1 mmol/L (70). In order to achieve those concentrations in the urine, a young adult with an average voiding rate of 6 x 300 mL per day would need to take more than 1 g of ketamine per session. These high doses of ketamine would need to be taken nearly daily so the bladder does not have time to repair itself. The highest esketamine dose used in the Phase 2 and Phase 3 clinical trials was 84 mg administered twice a week or at lower frequencies (weekly or twice weekly), ensuring a large margin of safety. With intermittent exposure, at the doses of 56 mg and 84 mg recommended in the summary of product characteristics for treatment of patients with TRD, it is considered that the bladder has sufficient time between dosing sessions for self-repair from any potential irritation. Further, notwithstanding the evidence of KIUT in ketamine abusers, there is no

evidence that repeated, pulsed administration of ketamine and/or esketamine treatment at subanesthetic doses in adults with mood disorders causes persistent interstitial cystitis (68). However, based on the literature interstitial cystitis was an AE of special interest and was assessed during the clinical trial program. It was included in the RMP as an important potential risk.

In the clinical trials symptoms of cystitis or lower urinary tract symptoms were monitored using Bladder Pain/Interstitial Cystitis Symptom score (BPIC-SS), which is a subject-reported outcome measure (71). The BPIC-SS includes 8 questions with a recall period of 7 days, giving a total score from 0 to 38. A total score of 19 or more has demonstrated good sensitivity/specificity and is considered a relevant cutoff to distinguish those with clinically significant bladder symptoms or cystitis. Subjects with a score >18 on the scale were further evaluated for interstitial cystitis and urinary tract infection.

Adverse events

The search strategy and a list of PTs returned by the search for the important risk of interstitial cystitis (long-term use) are: Allergic cystitis, Bladder fibrosis, Chemical cystitis, Cystitis, Cystitis erosive, Cystitis haemorrhagic, Cystitis Interstitial, Cystitis noninfective, Cystitis ulcerative, Cystitis-like symptom, Urinary bladder toxicity.

Across the studies no cases of ESK-NS related interstitial cystitis (including ulcerative cystitis) or cases suggestive of irreversible bladder damage were reported with esketamine treatment in long-term studies. However, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia and cystitis) in ESK-NS treated patients than in patients who received BPO-NS. Other reported urinary TEAEs included urinary tract infection, cystitis, cystitis bacterial, pyelonephritis and pyelonephritis acute. The events that were considered of clinical relevance, as they appeared to show a temporal relationship with esketamine administration in some subjects and were assessed by the investigators as drug-related, included urinary hesitation, oliguria, and urinary incontinence (44, 62).

Most of the patients that experienced a post-baseline increase in BPIC-SS score only had it at one time-point during the studies. The symptoms were typically mild to moderate in intensity and did not lead to discontinuation of treatment with ESK-NS. Clinical review of the data for all subjects with a score >18 on the BPIC-SS scale reported during the clinical studies of ESK-NS established that the urinary tract symptoms in general appeared to be reversible and did not suggest a risk of permanent bladder damage (44, 62).

Interstitial cystitis

As a higher rate of lower urinary tract symptoms occurred in ESK-NS treated patients than in PBO-treated patients, interstitial cystitis (long-term use) was included in the risk mitigation plan as important potential risk, requiring further evaluation via the SUSTAIN-3 study.

The frequency of TEAEs suggestive of interstitial cystitis in the All Clinical Trials Population (completed Phase 2 and 3 trials) was 0.7% (n=12). In The DB trials, only 3 cases (0.5%) were reported in the ESK-NS + OAD group vs. 1 case in the PBO-NS + OAD group (0.2%), which was below the expected incidence in the treated population. The OR (95% CI) of 2.6 (0.2, 134.8) indicated that there was insufficient evidence to support that the true OR of an interstitial cystitis-related event was great than 1 when comparing the ESK-NS + OAD group with POB-NS + OAD groups. None of the reported events in the DB trials (both treatment groups) and the All Clinical Trials Population was serious, and none was fatal. All reported events in the DB trials and the All Clinical Trials Population were mild or moderate in severity, with no severe events

reported (table 58) [redacted]

Table 58: Frequency (95% CI), Seriousness, Outcomes, and Severity of TEAEs Potentially Suggestive of Interstitial Cystitis in Clinical Trials (TRD)

	All Randomised, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD	Placebo + Oral AD	Esketamine + Oral AD
	(N=571)	(N=486)	(N=1,708)
Frequency	**n (%)**	**n (%)**	**n (%)**
Subjects With TEAEs Potentially Suggestive of Interstitial Cystitis[a]	**3 (0.5%)**	**1 (0.2%)**	**12 (0.7%)**
Odds ratio	2.6	-	-
95% CI[b]	0.2 to 134.8	-	-
Seriousness/Outcomes of Events[c]	**3**	**1**	**12**
Fatal	0	0	0
Serious	0	0	0
Recovered	2 (66.7%)	1 (100.0%)	10 (83.3%)
Recovered with sequelae	0	0	0
Recovering	1 (33.3%)	0	1 (8.3%)
Not recovered	0	0	1 (8.3%)
Unknown	0	0	0
Missing	0	0	0
Severity of Events[c]			
Mild	2 (66.7%)	1 (100.0%)	8 (66.7%)
Moderate	1 (33.3%)	0	4 (33.3%)
Severe	0	0	0
Missing	0	0	0

Note: MedDRA versions 18.0 (SYNAPSE) and 20.0 (TRANFORM-1, TRANFORM-2, SUSTAIN-1, SUSTAIN-2, and TRANFORM-3) were used to classify the adverse event information that is summarised in this table.

The following trials are included in the All Randomised, Blinded Trials Population: TRANFORM-1 (Double-blind Phase), TRANFORM-2 (Double-blind Phase), SUSTAIN-1 (Double-blind Maintenance Phase), TRANFORM-3 (Double-blind Phase), and SYNAPSE (Double-blind Phase excluding esketamine 14 mg). The following trials are

	All Randomised, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD	**Placebo + Oral AD**	**Esketamine + Oral AD**
	(N=571)	**(N=486)**	**(N=1,708)**
included in the All Clinical Trials Population: TRANFORM-1, TRANFORM-2, SUSTAIN-1, SUSTAIN-2, TRANFORM-3, and SYNAPSE (excluding Double-blind Phase esketamine 14 mg). Subjects in the All Randomised, Blinded Trials Population who were exposed to esketamine in trials TRANFORM-1 or TRANFORM-2 and transferred to SUSTAIN-1 and were re-randomised to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomised, Blinded Trials Population who received both esketamine and placebo in SYNAPSE in the Double-blind Phase were counted in both treatment groups. **Key:** AD=Antidepressant; CI=Confidence Interval; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Adverse Event; N=Number; TEAE=Treatment-emergent Adverse Event; TRD=Treatment-resistant Depression. a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'TEAEs Potentially Suggestive of Interstitial Cystitis'; the subject is counted only once regardless of the number of events or the number of occurrences. b: The 2-sided exact 95% CI in odds ratio of esketamine + oral AD to placebo + oral AD for All Randomised, Blinded Trials Population. c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'TEAEs Potentially Suggestive of Interstitial Cystitis' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarised.			

Given that no cases of esketamine-related interstitial cystitis were observed in any of the Phase 2 and Phase 3 clinical trials, which involved treatment for greater than 1 year, the impact on the risk benefit balance of the product is expected to be low. With intermittent exposure at the recommended doses of 28, 56, and 84 mg for TRD the bladder has sufficient time between dosing sessions for self-repair from any irritation.

6.1.13 Comparative analyses

ESK-NS (Spravato®) + a newly initiated OAD has been directly compared with OAD + NS-PBO in four Phase 3 clinical trials: three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3), and one maintenance study (SUSTAIN-1). As per the Handbook of the Medicines Council's process and methodologies for new pharmaceuticals and indication expansions version 2.4, a meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model. (72)
Forest plots available in section 8.3 show the risk ratio and mean difference results of the performed meta-analyses. All the I^2 statistic were less than 50% and chi-squared test were non-significant, thus the tests for heterogeneity does not indicate presence of heterogeneity (73). Consequently, the meta-analyses are all based on fixed effects estimates.

The absolute differences in effect were calculated using the estimated risk ratio (RR) from the meta-analyses as well as the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. (74)

For the long-term treatment efficacy, the long-term safety study SUSTAIN-2 and the TRD cohort study has been utilized to conduct an indirect treatment comparison. Detailed information regarding the methodology and the results are available in appendix 8.5, whereas the main results and conclusion are presented in this section.

The comparative results for clinical question 1 are summarized in table A4 of section 8.2 in the appendix.

The Phase 2 study, SYNAPSE was not included in the meta-analyses of the short-term studies and neither is comparative results from SYNAPSE presented in this section. This is due to SYNAPSE investigating esketamine nasal spray (as add-on to continued OAD) for the treatment of patients with moderate to severe MDD who failed to respond to at least 2 AD therapies during their current MDD episode (History of inadequate response to ≥2 ADs of which ≥1 AD was used in the current episode of depression). It should be noted that this inclusion criteria differs from the TRD definition as well as the populations studied in the Phase III trials. Furthermore, as participants in the SYNAPSE study continued their existing OAD treatment during the study, the intervention and comparator is not in line with the intervention and comparator in the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 as patient in the phase 3 trials initiated a new OAD in combination with either ESK-NS or PBO-NS.
However, the results from the SYNAPSE study are presented in section 6.1.9 as the Scientific Committee has expressed interest in the results of SYNAPSE and to underline and support the efficacy and safety of Spravato observed in the TRANSFORM studies.

MADRS total score at 6 months

Operationalisation of change in depressive symptoms measured according to MADRS total score and justification for the final estimation

The operationalisation of change in depressive symptoms measured according to MADRS total score and the justification for the final estimation for each study is described in the following.
MADRS is a validated instrument in depression that measures the change in symptoms and can quantify the severity of the depressive disorder. The MADRS is recorded at baseline and month 6 in the TRD cohort. In the SUSTAIN-2 study, the MADRS is recorded each week. The analysis time point at week 26 is used for the comparison with the TRD cohort. The analyses shown for the historical ITC are the change in depressive symptoms according to the MADRS total score as the difference in the mean change at week 26 from baseline for each treatment arm. The treatment effect is the mean difference between the treatment arms.

SUSTAIN-2

The endpoint change in depressive symptoms according to the MADRS total score is measured using the MADRS total score. SUSTAIN-2 is a non-randomised, single-arm, multicentre open-label study. Neither subjects nor practitioners were blinded for the intervention. All MADRS-based endpoints are analysed within the ITT population, which comprises all randomised subjects. The ITT principle is thus being adequately implemented for the MADRS-based endpoint. A comparison of the study protocol, statistical analysis plan and clinical study reports reveals no evidence of results-driven reporting. There are no indications for other aspects that might influence the risk of bias. Since SUSTAIN-2 is a single-arm study, there is no assessment of the risk of bias at endpoint level.

TRD cohort

The endpoint change in depressive symptoms according to the MADRS total score is measured using the MADRS total score. The TRD cohort is a prospective, non-interventional observational cohort study. Data that is available in the context of clinical practice, routine therapeutic procedures and diagnostic assessments will be collected. The criterion “adequate implementation of the ITT principle” is not applicable to the analysis of the registry data. The use of case report forms ensures consistent data collection. A comparison of the study protocol and clinical study report in the TRD cohort at study level reveals no evidence of result-driven reporting. Following the collection of baseline data, patients will participate in an observation period of at least 6 months to 21 months. Data will be collected for each patient after approximately 6 months. This collection is not event driven. In addition, due to any clinically relevant deterioration or improvement in the ongoing clinically depressive episode, data collection is event-driven during the observation period. The patient flow is shown in a transparent and comprehensible manner in the study. Other formal or technical aspects which could cause the results to be presented in a biased manner have not been identified. Since SUSTAIN-2 is a single-arm study, there is no assessment of the risk of bias at endpoint level.

Results for the ITC of SUSTAIN-2 and TRD cohort study

In the analysis of the endpoint MADRS total score change from baseline to *6 months,* a mean change from baseline of [redacted] is observed for patients in the SUSTAIN-2 study, see table 59. For the TRD cohort, a value of [redacted] is observed. [redacted]). Furthermore, the additional analyses presented in appendix 8.5 shows that there are consistent significant effects in favour of esketamine, regardless of the methodology used. Furthermore, additional sensitivity results based on a full BOCF approach and a histogram of estimated weights as well as description of the populations after weighting are available at section 8.5.24 and 8.5.15, respectively. This is delivered as requested by the Medicines Council during the validation process.

[redacted]

Serious adverse events at induction

The relative difference in RR between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the induction period is 1.398 (0.369-5.295). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 60.
In addition, the estimated difference on absolute effect is 0.4% (-0.07%-4.5%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 2.5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 4.5% is neither equal to; upper limit (UL) ≤ -2.5%-point nor is it equal to; UL < 2.5%-point and the lower bound of -0.7% is not equal to; LL > MKRF 2.5%-point.

Table 60: Clinically added value of ESK-NS in regards to SAEs at induction.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Adjusted least clinically relevant difference** -2.5%	**Estimated CI**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		0.4% (-0.7%-4.5%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		1.398 (0.369-5.295)

Serious adverse events at maintenance

Regarding the relative difference between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the maintenance period, the RR is 3.816 (0.432-33.739).
As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 61. In addition, the estimated difference on absolute effect is 1.9% (-0.9%-4.8%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 2.5%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 4.8% is neither equal to; upper limit (UL) ≤ -2.5%-point nor is it equal to; UL < 2.5%-point and the lower bound of -0.9%is not equal to; LL > MKRF 2.5%-point.

Table 61: Clinically added value of ESK-NS in regards to SAEs at maintenance.

Clinically added value – Serious adverse events		
Absolute difference - SAE	**Adjusted least clinically relevant difference -2.5%**	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		1.9% (-0.9%-4.8%)
Relative difference - SAE	**Specified confidence limit - SAE**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	

Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		3.816 (0.432-33.739)

Discontinuation due to adverse events at induction

The relative difference in RR between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients discontinuing treatment due to adverse events in the induction period is 2.598 (0.966-6.985). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 62.
In addition, the estimated difference on absolute effect is 2.8% (-0.1%-10.4%). Thus, the preliminary added value cannot be categorized. This is evident when the confidence interval around the absolute effect difference is compared with the adjusted least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 10.4% is neither equal to; upper limit (UL) ≤ -10%-point nor is it equal to; UL < 10%-point and the lower bound of -0.1% is not equal to; LL > MKRF 2.5%-point.

Table 62: Clinically added value of ESK-NS in regards to discontinuation at induction.

Clinically added value - Discontinuation		
Absolute difference – Discontinuation	**Adjusted least clinically relevant difference** -10%	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		2.8% (-0.1%-10.4%)
Relative difference - Discontinuation	**Specified confidence limit - Discontinuation**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		2.598 (0.966-6.985)

Discontinuation due to adverse events at maintenance

Regarding the relative difference between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients experiencing a SAE in the maintenance period, the RR is 1.272 (0.290-5.585). As the confidence interval of the relative difference does not correspond to any of the specified confidence limits as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, the preliminary clinically added value cannot be categorized, see table 63.
In addition, the estimated difference on absolute effect is 0.6% (-2.9%-4.0%). Thus, the preliminary added value falls under the category no documented added value. This is evident when the confidence interval

around the absolute effect difference is compared with the adjusted least clinically relevant difference of 10%-point and the criteria for the different preliminary categorize. More specifically the upper bound of 4.0% which is equal to; UL < 10%-point.

Table 63: Clinically added value of ESK-NS in regards to discontinuation at maintenance.

Clinically added value - Discontinuation		
Absolute difference – Discontinuation	**Adjusted least clinically relevant difference -10%**	**Estimated CI_high**
Merværdi af ukendt størrelse	UL ≤ -MKRF	
Ingen dokumenteret merværdi	UL < MKRF	0.6% (-2.9%-4.0%)
Negativ merværdi	LL > MKRF (statistisk signikant forskel)	
Kan ikke kategoriseres		
Relative difference - Discontinuation	**Specified confidence limit - Discontinuation**	**RR (CI)**
Stor merværdi	UL<0.75 og risiko >05%	
Moderat merværdi	0.75=<UL<0.90 eller (UL<0.75 og risiko < 5%)	
Lille merværdi	0.90 =< UL < 1.00 og LL =< 0.75	
Merværdi af ukendt størrelse	0.90 =< UL < 1.00 og LL<0.75	
Ingen dokumenteret merværdi	1.00=<UL<1.11 og LL=<1.00	
Negativ merværdi	LL>1.00	
Kan ikke kategoriseres		1.272 (0.290-5.585)

Narrative review of specific incidents, death for whatever reason and suicide attempts

See section 6.1.12 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

Remission at induction

The relative difference in RR between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients achieving remission at the end of the induction period at day 28 is 1.4 (1.163-1.860).
In addition, the absolute difference in effect following induction is 11.9% (4.1%-21.8%). The RR point estimate of 1.473 in favor of ESK-NS + OAD suggests that the likelihood of having remission at day 28 is 1.473 times higher when treated with ESK-NS + OAD compared to OAD + PBO-NS. Furthermore, as the lower confidence interval of the relative difference is above 1.11 the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 64. (74) The absolute effect point difference in favor of ESK-NS + OAD is close to the 15%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 4.1% is above the negative adjusted least clinically relevant difference (LL > -7.5%-point) but not equal to LL ≥ 7.5%-point, the preliminary categorization of clinically added value is no documented added value.

Table 64: Clinically added value of ESK-NS in regards to remission at induction.

Clinically added value - Remission		
Absolute difference - Remission	**Adjusted least clinically relevant difference – 7.5%**	**Estimated absolute difference (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	11.9% (4.1%-21.8%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	
Relative difference - Remission	**Specified confidence limit - Remission**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	1.470 (1.163-1.860)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	

Remission at maintenance

Regarding the relative difference between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients achieving remission at the end of the maintenance period for the stable remitters, the RR is 1.557 (1.163-2.084) whereas it for stable responders is 1.840 (1.103-3.068), see table 65.
In addition, the absolute difference in effect following maintenance is 23.3% (8.9%-37.7%) and 21.4% (4.7%-38.0%) for stable remitters and stable responders, respectively. The RR point estimates of 1.557 and 1.840 in favor of ESK-NS + OAD suggests that the likelihood of having remission at the end of the maintenance period is 1.557 and 1.840 times higher when treated with ESK-NS + OAD compared to OAD + PBO-NS for stable remitters and stable responders, respectively. Furthermore, as the lower confidence interval of the relative difference is above 1.11 for the stable remitters the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 65. (74) Furthermore, the preliminary clinically added value is of unknown size for the stable responders as the lower confidence interval is placed between 1.11 and 1.00, and the upper confidence interval is above 1.33
The absolute effect point difference of 23.3% for stable remitters and 21.4% for stable responders in favor of Spravato® + OAD is well above the 15%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 8.9% for stable remitters, is above the adjusted least clinically relevant difference (LL > 7.5%-point), the preliminary categorization of clinically added value is added value of unknown size. In contrary, the lower confidence interval of 4.7% for stable responders, results in the preliminary clinically added value being no documented added value.
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Table 65: Clinically added value of ESK-NS in regards to remission at maintenance.

Clinically added value - Remission			
Absolute difference - Remission	**Adjusted least clinically relevant difference – 7.5%**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF	23.3% (8.9%-37.7%)	
Ingen dokumenteret merværdi	LL > -MKRF		21.4% (4.7%-38.0%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		

Relative difference - Remission	Specified confidence limit - Remission	RR (CI) Stable remitters	RR (CI) Stable responders
Stor merværdi	LL>1.33		
Moderat merværdi	1.33 ≥ LL > 1.11	1.557 (1.163-2.084)	
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33		
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33		1.840 (1.103-3.068)
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00		
Negativ merværdi	UL<1.00		

Remission at 6 months – ITC of SUSTAIN-2 and the TRD cohort study.

Operationalisation of remission and justification for the final estimation

The operationalisation of remission according to MADRS and the justification for the final estimation for each study is described in the following.
In the SUSTAIN-2 study, remission is operationalised as the percentage of subjects who achieved an improvement in MADRS with a total score of 12 or fewer points during or after treatment with the study medication. In the TRD cohort, remission (contrary to the Phase-3 study programme, including the SUSTAIN-2 study) is operationalised as the percentage of subjects who achieved an improvement in MADRS with a total score of 10 or fewer points during or after treatment with the study medication. The MADRS is recorded at baseline and month 6 in the TRD cohort. In the SUSTAIN-2 study, the MADRS is recorded each week. The analysis time point at week 26 is used for the comparison with the TRD cohort.

To increase the comparability of SUSTAIN-2 and the TRD cohort in terms of remission the following analyses were used for the historical ITC:

- For SUSTAIN-2 the percentage of subjects with remission (MADRS total score ≤ 10 at week 26 was used instead of the phase-3 study programme defined remission(MADRS total score cut-off at ≤ 12.)
- For the TRD cohort study, the percentage of subjects with remission (MADRS total score ≤ 10) at 6 months was used.

Results for the ITC of SUSTAIN-2 and TRD cohort study

[redacted]

[redacted]

[redacted]		

Response at induction

The relative difference in RR between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients achieving response at the end of the induction period at day 28 is 1.379 (1.164-1.634).
In addition, the absolute difference in effect following induction is 14.4% (6.2%-24.1%). The RR point estimate of 1.379 in favor of ESK-NS + OAD suggests that the likelihood of having response at day 28 is 1.379 times higher when treated with ESK-NS + OAD compared to OAD + PBO-NS. Furthermore, as the lower confidence interval of the relative difference is above 1.11 the preliminary clinically added value is moderate as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 68. (74) Furthermore, as the lower confidence interval of the absolute difference of 6.2% is above the negative adjusted least clinically relevant difference (LL > -10%-point) but not equal to LL ≥ 10%-point, the preliminary categorization of clinically added value is no documented added value.

Table 68: Clinically added value of ESK-NS in regards to response at induction.

Clinically added value - Response		
Absolute difference - Response	**Adjusted least clinically relevant difference – 10%**	**Estimated (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	14.4% (6.2%-24.1%)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	
Relative difference - Response	**Specified confidence limit - Response**	**RR (CI)**
Stor merværdi	LL>1.33	
Moderat merværdi	1.33 ≥ LL > 1.11	1.379 (1.164-1.634)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33	
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00	
Negativ merværdi	UL<1.00	

Response at maintenance

Regarding the relative difference between ESK-NS + OAD and OAD + PBO-NS in the proportion of patients achieving response at the end of the maintenance period for the stable remitters, the RR is 1.349 (1.080-1.685) whereas it for stable responders is 1.951 (1.310-2.906), see table 69. In addition, the absolute difference in effect following maintenance is 19.5% (5.7%-33.3%) and 32.2% (15.4%-49.1%) for stable remitters and stable responders, respectively. The RR point estimates of 1.349 and 1.951 in favor of ESK-NS + OAD suggests that the likelihood of having remission at the end of the maintenance period is 1.349 and 1.951 times higher when treated with ESK-NS + OAD compared to OAD + PBO-NS for stable remitters and stable responders, respectively. Furthermore, as the lower confidence interval of the relative difference is placed between 1.33 and 1.11 the preliminary clinically added value is moderate for the stable responders as per the Handbook of the Medicine councils process and methodologies for new pharmaceuticals and indication expansions version 2.4, see table 69. (74) Furthermore, the preliminary clinically added value is of unknown size for the stable remitters as the lower confidence interval is placed between 1.11 and 1.00, and the upper confidence interval is above 1.33

The absolute effect point difference of 19.5% for stable remitters and 32.2% for stable responders in favor of ESK-NS + OAD is very close to and above the 20%-point difference defined as being the least clinically relevant difference. Furthermore, as the lower confidence interval of 15.4% is above the adjusted least clinically relevant difference (LL ≥ 10%-point), the preliminary categorization of clinically added value is added value of unknown size for stable responders. For stable remitters the lower limit confidence interval of 5.7% is above the negative adjusted least clinically relevant difference (LL > -10%-point).

Table 69: Clinically added value of ESK-NS in regards to response at maintenance.

Clinically added value - Response			
Absolute difference - Response	**Adjusted least clinically relevant difference – 10%**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF		32.2% (15.4%-49.1%)
Ingen dokumenteret merværdi	LL > -MKRF	19.5% (5.7%-33.3%)	
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		
Relative difference - Response	**Specified confidence limit - Response**	**RR (CI) Stable remitters**	**RR (CI) Stable responders**
Stor merværdi	LL>1.33		
Moderat merværdi	1.33 ≥ LL > 1.11		1.951 (1.310-2.906)
Lille merværdi	1.11 ≥ LL > 1.00 og UL ≤ 1.33		
Merværdi af ukendt størrelse	1.11 ≥ LL > 1.00 og UL > 1.33	1.349 (1.080-1.685)	
Ingen dokumenteret merværdi	0.90<LL=<1.00 og UL>=1.00		
Negativ merværdi	UL<1.00		

Response at 6 months – ITC of SUSTAIN-2 and the TRD cohort study.

[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	

Quality of life at induction

The mean difference change in health status index from baseline to the endpoint of the double-blind induction between ESK-NS + OAD and OAD + PBO-NS of 0.054 (0.017-0.092) demonstrate an improvement in quality of life in patients with TRD. However, as the lower confidence interval of the absolute difference of 0.021 is above the negative adjusted least clinically relevant difference (LL > -0.035 points) but not equal to LL ≥ 0.035 points, the preliminary categorization of clinically added value is no documented added value, see table 72.

Table 72: Clinically added value of ESK-NS in regards to EQ-5D at induction.

Clinically added value - EQ-5D		
Absolute difference – EQ-5D	**Adjusted least clinically relevant difference – 0.035 points**	**Estimated (CI)**
Merværdi af ukendt størrelse	LL ≥ MKRF	
Ingen dokumenteret merværdi	LL > -MKRF	0.054 (0.017-0.092)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)	

Quality of life at maintenance

The mean difference change in health status index from baseline of the maintenance phase to the endpoint of the maintenance phase between ESK-NS + OAD and OAD + PBO-NS of 0.029 (-0.011-0.069) and 0.050 (0.010-0.090) demonstrate an improvement in quality of life in patients with TRD. However, as the lower confidence interval of the absolute difference of -0.011 for stable remitters and 0.010 for stable responders is above the negative adjusted least clinically relevant difference (LL > -0.035 points) but not equal to LL ≥ 0.035 points, the preliminary categorization of clinically added value is no documented added value, see table 73.

Table 73: Clinically added value of Spravato® in regards to EQ-5D at maintenance.

Clinically added value - EQ-5D			
Absolute difference – EQ-5D	**Adjusted least clinically relevant difference – 0.035 points**	**Estimated (CI) Stable remitters**	**Estimated (CI) Stable responders**
Merværdi af ukendt størrelse	LL ≥ MKRF		
Ingen dokumenteret merværdi	LL > -MKRF	0.029 (-0.011-0.069)	0.050 (0.010-0.090)
Negativ merværdi	UL < -MKRF (statistisk signikant forskel)		

6.1.14 Other considerations

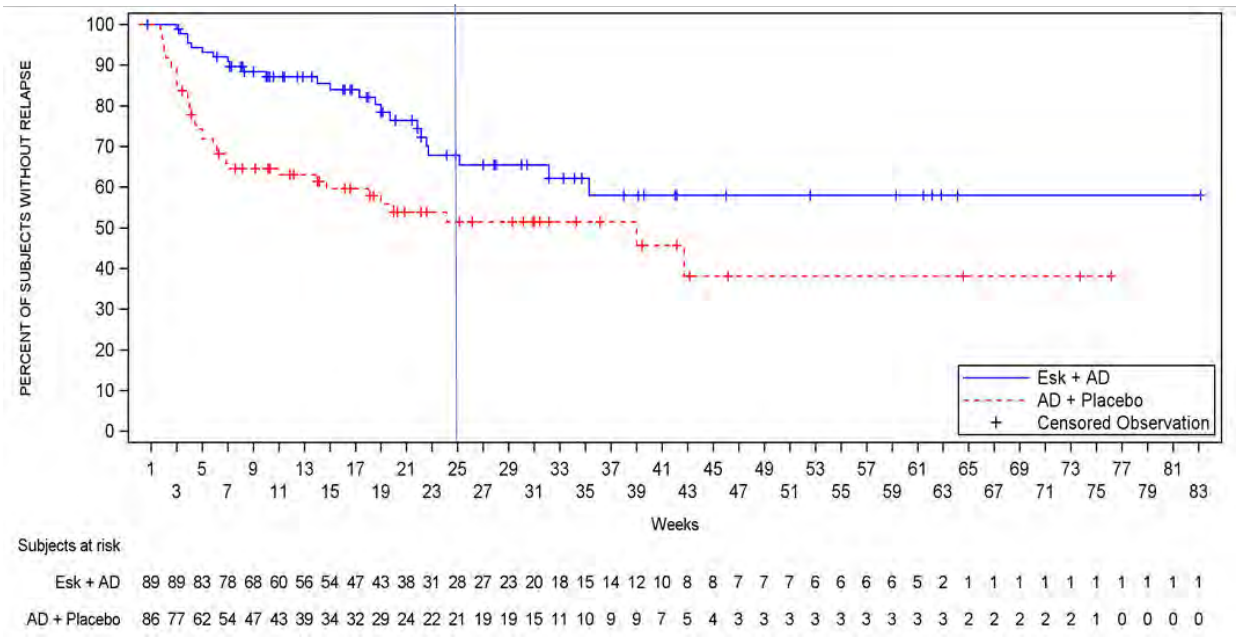
Treatment length

For the patients who achieve response or remission at the end of the induction phase (4 weeks), as stated in the SmPC, it is expected that they will discontinue esketamine nasal spray when there is no clinical need for further treatment (treatment is recommended for at least 6 months with the need for continued treatment re-examined periodically as stated in the SmPC). In clinical practice, it is expected that physicians would aim to reduce the esketamine nasal spray treatment length as much as possible based on individual patient needs. But as TRD patients have a severe depression (long time since first diagnosis and long/recurrent episodes), it is expected that the majority of patients will require ESK-NS treatment for 6-12 months.

In average 9 months (approx. 36 weeks) after the induction phase is defined as the timepoint of recovery, hence the time a patient can stop esketamine treatment. This 36 weeks definition (recovery definition) was supported by clinical data on relapse among stable remitters from the SUSTAIN-1 trial.
SUSTAIN-1 consisted of an open-label induction phase (4 weeks; direct-entry patients only), an optimisation phase (12 weeks; both direct-entry and transferred-entry patients), and a double-blind maintenance phase. After 24 weeks of maintenance therapy, patients showed a reduced risk of relapse, see figure 23. This corresponds to 36 weeks after the induction treatment period (12 weeks optimization + 24 weeks maintenance). Thus, patients before this timepoint are in remission and are subject to higher relapse risk compared to patients who had passed 36 weeks post-acute treatment, where their relapse risk is lower.(17)

Conclusive we assume the treatment length of Spravato® in combination with a SSRI or SNRI to be 4 weeks of induction + approx. 36 weeks of maintenance treatment as the clinicians can be more certain that the patients will remain stable after the discontinuation of Spravato®.

Figure 23: Kaplan-meier curve over proportion of patient who remained relapse-free/stable remitters(17)



Reflections related to practical aspect of Spravato® administration

ESK-NS is intended to be self-administered by the patient under the direct supervision of a healthcare professional (HCP) as ESK-NS has been reported to cause adverse events during the clinical trials that may include blood pressure, impaired attention, judgment, thinking, reaction speed and motor skills. Therefore, patients should be monitored under the supervision of an HCP at each treatment session to assess when the patient is considered stable and ready to leave the clinic based on clinical judgement and the risk minimization document "ready to leave checklist" (5) A post hoc analysis observed that ≥90% of patients were considered ready for discharge at 90 minutes after ESK-NS administration. (75) Furthermore, based on the trial investigators' experience, the supervision of self-administration of a group of six patients in a clinic could be managed by one or two nurses. (41)

There is also attached a benefit to the direct supervision by an HCP as it ensures proper guidance and support of the patient during the self-administration of esketamine as well as compliance transparency with the treatment. (5)

Further, direct supervision is already a well-known and common set-up for certain treatments in Danish psychiatry. Treatment with the long-acting antipsychotic olanzapine pamoate require observation after each injection in a health care facility by appropriately qualified personnel for at least 3 hours. In addition, ECT requires preliminary examination, anesthesia, electric current treatment and post-treatment observation time (usually 30-60 min at the observation ward). Thus, Danish psychiatry already has the needed infrastructure to initiate and conduct ESK-NS treatment.(76)

From a patient perspective we recognize that the supervision required at each administration session could interfere with patients' everyday life, especially during the initial induction phase (first 4 weeks). However, in this context it is equally important to emphasize the suffering caused by an insufficiently treated TRD. TRD is a severely debilitating and potentially life-threatening disease. Symptoms include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy usual activities, and feelings of worthlessness. These symptoms result in an impaired capacity and inability to work, to the point of complete inability to function, which substantially interferes with social connection, integration and relationships. (7)
Thus, the possible benefit of ESK-NS treatment has been a key driver for many patients' engagement in the esketamine trials as it has outweighed the need for regular visits.

Reflections related to compliance

With respect to the raised concern regarding lack of compliance, data from the long-term study SUSTAIN-1 showed that no patients were withdrawn from the esketamine treatment group during the maintenance phase due to non-compliance. (40) These results underline that patients with a satisfying initial treatment response are prone to adhere to the treatment. As the treatment with esketamine requires supervision, any potential compliance issues will be fully transparent to the HCP and allow them to act accordingly to avoid any serious consequences for the patient. (5)

Secondly, ketamine, the racemic mixture of arketamine and esketamine, is listed as a narcotic agent in Denmark with a well-known potential for recreational abuse. ESK-NS contains esketamine however, there were no reports of drug-seeking behavior (e.g. requests for dosing changes and/or diversion of Spravato®), no reports of patients requesting an increase in dose or dosing frequency (a potential early indicator of

drug-seeking behavior) or evidence of a distinct withdrawal syndrome after cessation of treatment (PWC-20 results) in the Phase 3 clinical trials of ESK-NS (for further details, see section on Substance abuse) (5, 77) To minimize any potential risk of abuse, misuse and diversion associated with the self-administration of ESK-NS the product is to be administered under the direct supervision of an HCP.
Whether any patients would initiate self-medication with illegal ketamine caused by lack of compliance during continuous treatment cannot be excluded. However, the illicit use of ketamine has been reported on a relatively small global scale for several decades. (78) In line with this the Danish Health Authorities conducted a survey in 2017 concluding that only 2% of all respondents aged 16-44 years had experience with the illicit use of ketamine, whereas persons above 44 years were excluded due to a very limited use of illegal drugs. (79) These data underlines that ketamine is not a commonly misused drug in Denmark, which reduces the overall risk of self-medication. Further, to minimize the risk of any drug abuse related to ESK-NS treatment, risk minimization material for all psychiatrists has been provided addressing how to carefully assess each patient's risk for abuse and misuse prior to prescribing ESK-NS. This information also increase the awareness among HCPs to monitor each patient for signs of drug abuse. Based on this we find it unlikely that well-treated patient would discontinue ESK-NS and initiate illicit ketamine self-medication. (5, 77)

Substance abuse

Abuse potential

Ketamine and esketamine are non-competitive, non-selective NMDA receptor antagonists well-known for their psychoactive effects and recreational abuse potential (80). During the clinical development program the sponsor prospectively monitored and assessed events of abuse potential. This analysis evaluated all studies for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes. A positive signal from abuse-related AEs does not inherently mean that a test drug has abuse potential. The search terms are based on compilation of abuse-related AE terms, related to the drug's pharmacology, as provided in the MedDRA System Organ Classifications (44).

Drug abuse potential is considered an important identified risk for esketamine in the risk management plan (RMP) that are well-characterized and mitigated through comprehensive risk minimization and pharmacovigilance activities described in the RMP.

In a single-dose, double-blind, double-dummy, placebo-controlled, randomized crossover study (TRD1015) of abuse potential conducted in recreational, nondependent, polydrug users (n=34), single doses of ESK-NS (84 and 112 mg) and the positive control drug, intravenous ketamine (0.5 mg/kg infused over 40 minutes) produced significantly greater scores than placebo on subjective ratings of "drug liking at the moment" and other measures of subjective drug effects, which suggests that the potential for abuse is similar to that of ketamine (62, 81) . However, the illicit use of ketamine has been reported in the literature at doses between 0.125-3 g per session (67) with an average of 2.77 g for an average of 20 days/months (66), which is at a much higher dose and frequency than recommended for ESK-NS.

Further, despite its abuse potential, the illicit use of ketamine has been reported low at a global scale (82). In line with these observations the misuse of ketamine is limited in the background population according to data from the Danish Health Authorities (0.4% among adults aged 18-44 years). This underlines that ketamine is not a commonly misused drug in Denmark (83).

Across the completed phase 3 studies in TRD, there were no reports of patients requesting an increase in dose or dosing frequency (a potential early indicator of drug-seeking behaviour). Review of study accountability records also showed that ESK-NS kits for each patient were inventoried and accounted for throughout. There were no confirmed cases of drug diversion in the completed Phase 3 studies.

Data from all clinical trials with ESK-NS were examined for the occurrence of adverse events related to the CNS that were suggestive that the drug might specifically be sought by patients for abuse purposes. Such potential abuse-related terms are related to esketamine's pharmacology and were identified prior to the start of the Phase 3 program based on the known properties of esketamine and ketamine. (44).

Adverse events

Across all completed phase 2 and 3 studies, PT searches did not yield any reported TEAEs of *drug abuse, drug abuser, drug dependence, drug detoxification, drug rehabilitation, drug tolerance, drug tolerance increased, or drug use disorder*. There were no reports from the investigational sites of any subjects requesting an increase in either the dose of esketamine or in the frequency of treatment sessions (as a potential early indicator of drug-seeking behavior) (44).

Overall, the frequency of reported TEAEs suggestive of drug abuse was 54.4% in the All Clinical Trials Population (Completed Phase 2 and 3 trials), and 4.0 times higher in the ESK-NS + OAD group vs. PBO-NS+OAD group in the double-blind (DB) trials (51.1% vs. 12.8%). The odds ratio (OR) of 7.2 (95% confidence interval [5.2; 9.9] indicated that the odds of a TEAE suggestive of drug abuse occurring in the ESK-NS+ OAD group was 7.2 times that of the PBO-NS + OAD group (table 74). In the DB trials, no fatal events were reported in either group, only a single serious event was reported in the PBO-NS + OAD group vs. no cases in the ESK-NS + OAD group. In the All Clinical Trials Population , 4 (0.2%) events were serious and none was fatal. The investigator assessed both events as not related to the study drug and both events resolved. In the DB trials, 93.1% of the events were mild or moderate in severity, with 6.9% of the events were severe. Across all completed trials of ESK-NS in TRD, TEAEs suggestive of drug abuse most commonly associated with ESK-NS included dizziness, somnolence, and dissociation. In the fixed-dose short-term trial TRANSFORM-1, a higher incidence of dissociation was observed with the higher ESK-NS dose; the other commonly reported TEAEs suggestive of drug abuse did not show a dose effect. Across the completed TRD trials, the majority of TEAEs suggestive of drug abuse were transient and self-limiting, occurring and resolving on the day of dosing of ESK-NS, and mild or moderate in severity (44).

In line with the above, the interim report of the long-term extension safety study SUSTAIN-3 found that the most commonly reported (≥10% of subjects) TEAEs suggestive of abuse potential during the combined IND and OP/MA phases were dizziness (31.9%), dissociation (24.4%), and somnolence (22.5%). These events were generally transient events that are known to be related to the mechanism of action of esketamine. In SUSTAIN-3 there were 2 serious TEAEs suggestive of abuse potential (confusional state- 2 subjects). The investigator assessed both events as not related to the study drug and both events resolved. In general, for all of the TEAEs that occurred on the day of dosing, most (>97%) resolved the same day with the exception of auditory hallucinations (5 of 8 subjects [62.5%] had resolution on same day). Two subjects experienced drug withdrawal syndrome, both of which were considered by the investigator as not related to study drug. The verbatim terms were "withdrawal syndrome due to duloxetine" and "venlafaxine withdrawal symptoms". One subject experienced an event of drug abuse. The verbatim term was "laxative abuse"(46).

Table 74: Frequency (95% CI), Seriousness, Outcomes, and Severity of Treatment-emergent Adverse Events Suggestive of Drug Abuse in Clinical Trials (TRD) (44).

	All Randomised, Blinded Trials Population		All Clinical Trials Population
	Esketamine + Oral AD	Placebo + Oral AD	Esketamine + Oral AD
	(N=571)	(N=486)	(N=1,708)
Frequency	**n (%)**	**n (%)**	**n (%)**
Subjects With TEAEs Suggestive of Drug Abuse[a]	**292 (51.1%)**	**62 (12.8%)**	**930 (54.4%)**
Odds ratio	7.2	-	-
95% CI[b]	5.2 to 9.9	-	-
Seriousness/Outcomes of Events[c]	**478**	**85**	**1,601**
Fatal	0	0	0
Serious	0	1 (1.2%)	4 (0.2%)
Recovered	474 (99.2%)	83 (97.6%)	1,582 (98.8%)
Recovered with sequelae	3 (0.6%)	0	5 (0.3%)
Recovering	1 (0.2%)	1 (1.2%)	4 (0.2%)
Not recovered	0	1 (1.2%)	10 (0.6%)
Unknown	0	0	0
Missing	0	0	0
Severity of Events[c]			
Mild	250 (52.3%)	63 (74.1%)	898 (56.1%)
Moderate	195 (40.8%)	19 (22.4%)	605 (37.8%)
Severe	33 (6.9%)	3 (3.5%)	98 (6.1%)
Missing	0	0	0

Note: MedDRA versions 18.0 (SYNAPSE) and 20.0 (TRANSFORM-1, TRANSFORM-2, SUSTAIN-1, SUSTAIN-2, and TRANSFORM-3) were used to classify the adverse event information that is summarised in this table.

The following trials are included in the All Randomised, Blinded Trials Population: TRANSFORM-1 (Double-blind Phase), TRANSFORM-2 (Double-blind Phase), SUSTAIN-1 (Double-blind Maintenance Phase), TRANSFORM-3 (Double-blind Phase), and SYNAPSE (Double-blind Phase excluding esketamine 14 mg). The following trials are included in the All Clinical Trials Population: TRANSFORM-1, TRANSFORM-2, SUSTAIN-1, SUSTAIN-2, TRANFORM-3, and SYNASPE (excluding Double-blind Phase esketamine 14 mg).

Subjects in the All Randomised, Blinded Trials Population who were exposed to esketamine in trials TRANSFORM-1 or TRANSFORM-2 and transferred to SUSTAIN-1 and were re-randomised to placebo for the Double-blind Maintenance Phase were counted in both treatment groups. Subjects in the All Randomised, Blinded Trials Population who received both esketamine and placebo in SYNAPSE in the Double-blind Phase were counted in both treatment groups.

The All Randomised, Blinded Trials Population includes the first 2 weeks of the Follow-up phases for each of the trials listed, except for SYNAPSE; for SYNAPSE, the Follow-up data are included only for those subjects that did not enter the Open-label Phase.

Key: AD=Antidepressant; CI=Confidence Interval; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of Adverse Event; N=Number; TEAE=Treatment-emergent Adverse Event; TRD=Treatment-resistant Depression.

a: Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under 'TEAEs Suggestive of Drug Abuse'; the subject is counted only once regardless of the number of events or the number of occurrences.

b: The 2-sided exact 95% CI in odds ratio of Esketamine + Oral AD to Placebo + Oral AD for All Randomised, Blinded Trials Population.

c: The total number of distinct preferred terms (ie, preferred terms that refer to separate adverse events reported by individual subjects) in the 'TEAEs Suggestive of Drug Abuse' group by seriousness/outcome and also by severity. For a given preferred term, the most severe event is summarised.

Dependence and withdrawal

Dependence and attenuation have been reported in the literature with prolonged use of ketamine. Individuals who were using high doses on a frequent basis and considered dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations. However, no specific ketamine withdrawal syndrome has yet been confirmed (50).

In the completed Phase 2 and phase 3 trials the Physician Withdrawal Checklist 20-Item (PWC-20) was administered to assess potential withdrawal symptoms following cessation of ESK-NS treatment. The PWC-20 was measured at the 1- and 2-week follow-up visits in TRANSFORM-1,2,3 and SUSTAIN-1, and at 1-, 2- and 4-week follow-up visits in SUSTAIN-2. Given the short half-life of esketamine, a 2-week follow-up was expected to be sufficient to assess potential symptoms of withdrawal. The categories of withdrawal symptom status were as follows: no symptoms; improved; symptom present, unchanged; and new or worsened symptom (62).

Across trials, most subjects did not report symptoms on the PWC-20. Reported symptoms were primarily mild to moderate in severity. New or worsening symptoms that generally corresponded to worsening of depression occurred after withdrawal of treatment. Worsening of depression symptoms was observed mostly in subjects, who discontinued treatment due to lack of therapeutic response. Across TRD trials, commonly reported symptoms following discontinuation of ESK-NS were anxiety/nervousness, fatigue/lethargy/lack of energy, difficulty concentrating/remembering, dysphoric mood, depression, and irritability. In the clinical trials including OAD + PBO-NS as a comparator, the same symptoms were also frequently reported by subjects following discontinuation of placebo. The reported symptoms were consistent with those of depression and anxiety (62).

With focus on long-term studies, the SUSTAIN-1 study reported no difference between treatment arms (ie, ESK-NS + OAD vs PBO-NS + OAD) for each of the 20 items on the PWC-20 scale, which underlines that there is no evidence suggestive of a distinct withdrawal syndrome 1 or 2 weeks after cessation. More specifically, relative to the end of the MA phase of the study there were no new or worsened symptoms that were reported on the PWC-20 at the incidence exceeding 25% either at the 1-week FU visit or at the end of FU visit in either treatment group. At the Week 1 FU visit, most new or worsened symptoms were reported at slightly higher rates (<5% difference) in subjects previously treated with ESK-NS + OAD than OAD + PBO-NS. At the Week 2 FU visit, new or worsened symptoms were reported by <25% of subjects in either treatment group, with the exception of anxiety-nervousness (26.7% and 25.8%, respectively). This suggest that the drug abuse potential for patients with TRD alone is low (44).

In the OL long-term safety study SUSTAIN-2 most subjects did not report symptoms on the PWC-20. Most of the reported symptoms were mild to moderate. For subjects who discontinued from the IND phase, the most common new or worsening symptoms (>20% of subjects) at Week 1 of the 4-week FU phase were: irritability (37.1%, 23 subjects), anxiety-nervousness (29.0%, 18 subjects), and fatigue-lethargy-lack of energy (22.6%, 14 subjects). The most common new or worsening symptoms (>20% of subjects) at the endpoint of the 4-week FU phase were anxiety-nervousness (29.5%, 36 subjects), irritability (28.7%, 35 subjects), difficulty concentrating, remember (25.4%, 31 subjects), insomnia (23.8%, 29 subjects), restlessness-agitation (23.0%, 28 subjects), and loss of appetite (20.5%, 25 subjects). These symptoms, observed at the end of the IND phase, were likely a reflection of underlying depressive symptoms that have not improved in subjects who did not respond to treatment. For subjects who discontinued from the OP/MA phase, the most common new or worsening symptom (>20% of subjects) was fatigue-lethargy-lack of energy (25.0%, 13 subjects) at Week 1 of the 4-week FU phase. The most common new or worsening

symptom (>20% of subjects) at the endpoint of the 4-week FU phase was insomnia (22.7%, 20 subjects) (44).

Patients with comorbid TRD and substance or alcohol abuse disorders have not been studied; therefore, the risk in this population is unknown. The available data from patients with TRD suggest no significant impact on the risk-benefit balance of ESK-NS. The SmPC and PL, as well as the RMP material (HCP guide and patient guide), provide information to the prescriber and the patient on the risk of abuse. Prescribers are advised that individuals with a history of drug abuse or dependence may be at a greater risk for abuse and misuse of ESK-NS and that individuals should be assessed prior to treatment for a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended as signs may develop particularly when not used as prescribed (eg, taking high doses on a daily basis over an extended period of time) or in individuals with a history of drug abuse or dependence (62).

To minimize any potential risk of abuse, misuse and diversion associated with the self-administration of ESK-NS the product is available by special and restricted medical prescription only and should be administered under the direct supervision of an HCP. The recommended dosing of esketamine nasal spray twice weekly for 4 weeks, followed by weekly or every-other week dosing for patients with a favorable clinical response. During the longer-term treatment, physicians are recommended to individualize the dosing frequency to the lowest frequency needed to maintain the patient's clinical response and to perform periodic re-evaluation of patients to determine the need for continued treatment. The risk for drug abuse is mitigated with appropriate warnings and instructions in the EU product information (EU PI) (ie, Summary of Product Characteristics (SmPC) and package leaflet [PL]), limited pack sizes and legal controls determined by the dispensing code A**§4**-BEGR in Denmark. In addition, clinicians and patients will be provided with instructions in the RMP material (HCP guide and patient guide) for minimizing the risk of drug abuse. Further, the drug product is contained in a Type I glass vial sealed with a cholorobutyl rubber stopper. The filled and stoppered vial is seated into a container holder assembled into a manually activated nasal spray device. The device is difficult to disassemble due to interlocking design features of the actuator subassembly. Attempts to break open the device damage the vial and the contents are lost. The force required to pull the device apart is at least 60 Newtons (~13 pounds). If the device is taken apparat, the stoppered vial provides an additional challenge to disassembly, as it is very difficult to pull the stopper out. Breaking the vial instead results in loss of the contents. The product is supplied as a single-use device containing a total of 32.3 mg of esketamine HCl (equivalent to 28 mg of Esketamine). When manually actuated, the device dispenses 2 individual sprays; no sprays remain after the second spray is actuated. The nasal spray device has a nominal fill volume of 230 µL. The average measured residual volume left in the

nasal spray device after actuation is ~ 30 µL (4 mg base). Based on the above provided information, the impact of drug abuse on public health is expected to be low (62).

Summary of registered manic events during treatment and follow-up.

Emergence of symptoms of hypomania or mania have been reported with the use of oral AD in patients with MDD. Emergence of such symptoms may be related to undiagnosed bipolar disorder.(84, 85)

Patients with current or prior DSM-5 diagnosis of bipolar disorder or related disorders (as assessed by the Mini International Neuropsychiatric Interview [MINI]) were excluded from enrollment in the esketamine clinical phase 3 trials. Further, the use of lithium, anticonvulsants (valproate, carbamazepine), and antipsychotics were prohibited during the study.

In the phase 3 esketamine clinical trial program, the observed rate of mania/hypomania was <0.5%. A confounding factor was all subjects initiated a newly initiated OAD at the time of study entry. Across completed phase 2 and 3 studies, treatment-emergent adverse events (TEAEs) of mania/hypomania were reported in 2 patients exposed to ESK-NS + OAD (case 1 and case 2). (1) A third subject was reported to have hypomania during the study (case 3) but was defined as euphoria instead during follow-up by investigator.

Below in table 75 and 76 is a list of the reported treatment emergent adverse events of mania/hypomania in the clinical phase 3 trial program of esketamine (Short-term trials: TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3) (Long-term trial: SUSTAIN-1) during treatment and follow-up periods that included OAD + PBO-NS. A short description of each of the individual cases is also presented. (40)

Table 75: Treatment emergent adverse events of mania/hypomania in TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 (1)

Short-term trials						
TEAE; Mania	**TRANSFORM-1**		**TRANSFORM-2**		**TRANSFORM-3**	
	Esk-NS+oAD (n=231)	PBO+oAD (N=113)	Esk-NS+oAD (n=116)	PBO+oAD (n=111)	Esk-NS+oAD (n=72)	PBO+oAD (n=66)
Treatment	1 (0.4%)	0	0	0	0	0
Follow-up	0	0	0	0	0	0

Table 76: Treatment emergent adverse events of mania/hypomania in SUSTAIN-1 (40)

Long-term trial							
TEAE; Mania/hypomania	**SUSTAIN-1 (OL Induction Phase)**	**SUSTAIN-1 (optimization phase)**		**SUSTAIN-1 (Db Maintenance phase)**		**SUSTAIN-1 (Follow-up Phase)**	
	Esk-NS+oAD (n=437)	Esk-NS+oAD (n=455)	PBO+oAD (n=86)	Esk-NS+oAD (n=152)	PBO+oAD (n=145)	Esk-NS+oAD (n=481) for any phases	PBO+oAD (n=64) for any phases
Treatment	1 (0.2%)	0	0	0	0	-	-
Follow-up	-	-	-	-	-	1 (0.2%)	0

Safety analysis set

TRANSFORM-1: short description of case

- Case 1 (Mania): There was 1 reported AE of mania in a male on day 2 of the double-blind induction phase in a short-term phase 3 trial (TRANSFORM-1). The patient had received esketamine 56 mg + newly initiated daily duloxetine 60 mg the previous day. This AE led to withdrawal from the study, was resolved on day 7 without treatment, and was assessed as probably related to esketamine by the investigator. The investigator confirmed the subject had no prior history of bipolar disorder, no family history of bipolar disorder and no history of drug or alcohol use prior to the visit. (40)

SUSTAIN-1: short description of cases

- Case 2 (Mania): One direct-entry male subject, with no family history of bipolar disorder, was withdrawn from the induction phase at day 31 as he did not meet the criteria for continuing into the next phase. The subject had received eskteamin 56 mg + newly initiated daily sertraline 50 mg on day 1, was increased to 84 mg esketamine on day 5. The subject entered into the follow-phase by Day 32 and started experiencing depressive symptoms and was hospitalized on day 35 due to worsening symptoms. At the time, the patient was on sertraline 200 mg daily, and the dose was reduced to 100 mg daily on day 37. On day 38, the patient's depression resolved, however a manic episode was reported the same day. Medications administered during the manic episode included sertraline, valproic acid, haloperidol, olanzapine, clonazepam, and lithium carbonate. The last dose of sertraline was on day 42, and the patient completed the follow-up phase on day 43. On day 65, the mania resolved, and the patient was discharged. This AE was assessed as not related to esketamine by the investigator and possibly related to sertraline. (40)

- Case 3 (euphoria): One direct-entry subject experience 4 separate adverse events (Day 1, 4, Day 18 and Day 25) that were initially reported as hypomania (moderate: first 3 events; mild: one event) in the open-label induction phase in a long-term relapse prevention study (SUSTAIN-1). However, on follow-up the investigator clarified that the symptoms lasted only 30 minutes on each occasion and agreed these events would be better defined as euphoria. This subject had no personal or family history of bipolar disorder. (40)

[redacted]

Overall, there was insufficient evidence to associate administration of ESK-NS with an onset of acute mania or hypomania.

[redacted]

Data on co-morbidities among patients at study inclusion

Subjects with a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorder (confirmed by the MINI), comorbid obsessive-compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8 and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder were excluded from the phase 3 clinical esketamine trials.

The pooled incidence of common psychiatric comorbidities upon enrollment in the phase 3 TRD trials in adults 18-64 years (TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1) and separately in adults ≥65 years (TRANSFORM-3) is presented in the table 77 below. Results of the Mini-International Neuropsychiatric Interview (MINI) was used to identify the presence of comorbid psychiatric conditions. This diagnostic interview was conducted at the site at the first screening visit to conform patient eligibility. (40)

Table 77: Pooled incidence of common psychiatric comorbidities upon enrollment in TRANSFORM-1, TRANSFORM-2 and SUSTAIN-1 and incidence in TRANSFORM-3. (40)

	Pooled Incidence (TRANSFORM-1, TRANSFORM-2 & SUSTAIN-1) ESK patients (n=773)	TRANSFORM-3 ESK patients (n=72)
Generalized Anxiety Disorder	9.2% (n=71)	13.9% (n=10)
Panic Disorder	5.4% (n=42)	5.6% (n=4)
Social Anxiety Disorder	4.7% (n=36)	5.6% (n=2)
Agoraphobia	4.5% (n=35)	2.8% (n=2)
Posttraumatic Stress Disorder	1.6% (n=12)	0

Additionally, a pooled post hoc analysis of TRANSFORM-1 and TRANSFORM-2 looked at patients with TRD and comorbid anxiety at baseline based on 3 definitions: 1) presence of anxious depression, based on the Inventory of Depressive Symptomatology – Clinician rating (IDS-C) anxiety subscale (IDS-C_{ANX}) score ≥8; 2) comorbid anxiety disorder as evaluated by the Mini-International neuropsychiatric Interview (MINI); and 3) presence of anxious distress, based on a score ≥2 on at least 2 items of GAD-7 scale among the following items: item 1 (feeling anxious), 2 (unable to stop worrying), 5 (restlessness), and 7 (being afraid). At baseline, 22.3% (126/564), 14.2% (80/565) and 72.9% (412/565) of patients had anxious depression, comorbid anxiety disorder, or anxious distress, respectively. (86)

The proportion of comorbid psychiatric disorders in TRD patients of the clinical esketamine trial program is in line with a recent Swedish register-based cohort study reporting a psychiatric comorbidity of 26.4% among TRD patients (87) Further, the presence of comorbid anxiety disorder (14.2%) among TRD patients in the clinical trials is consistent with another recent Danish register-based cohort study (14.9%) (9). Thus, the TRD patient population included in the clinical trials has comparable psychiatric comorbidities with the general TRD population.

No summary data of somatic comorbidities were available from the clinical trials. Thus, it is only the psychiatric comorbidities that are presented in this section.

Data on average remission and response scores over time during treatment and follow up

Data on average remission and response scores over time are presented from the long-term relapse prevention study (SUSTAIN-1) in the below figure 25a and 25b (a: Patients who were stable Remitters; b: Patients who were stable Responders). (88)

Figure 25a: Mean (± SE) in MADRS total score over time LOCF during the Induction, optimization and maintenance Phases in patients who were Stable Remitters (88)

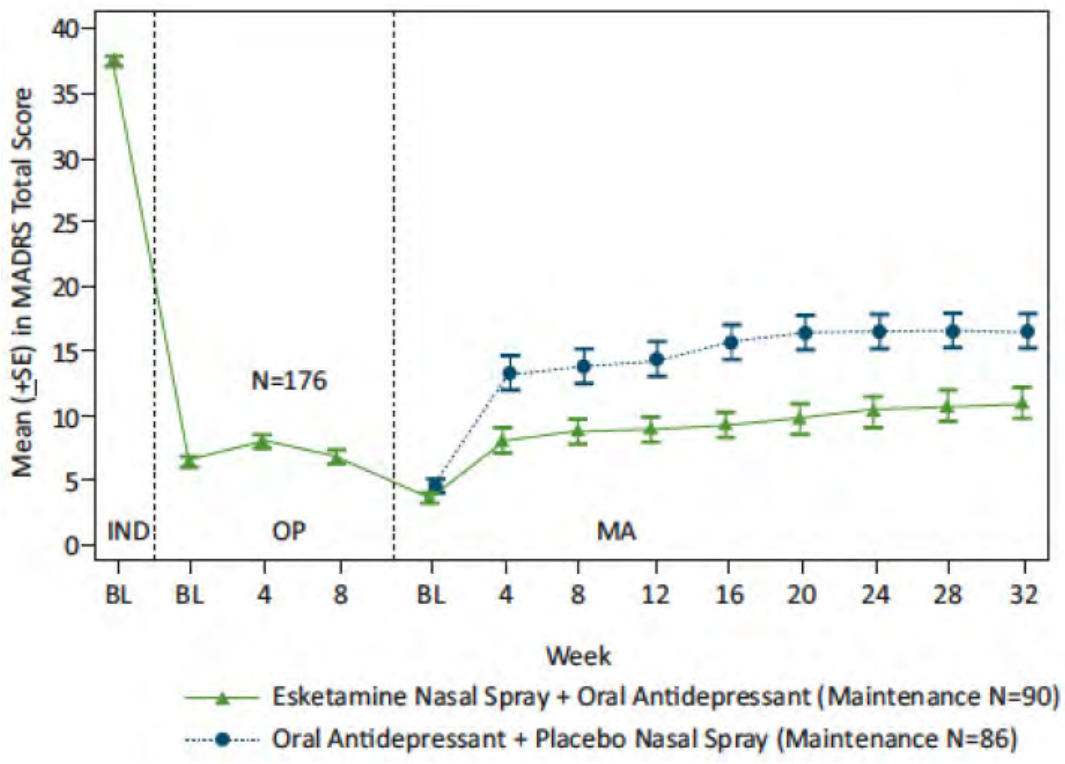
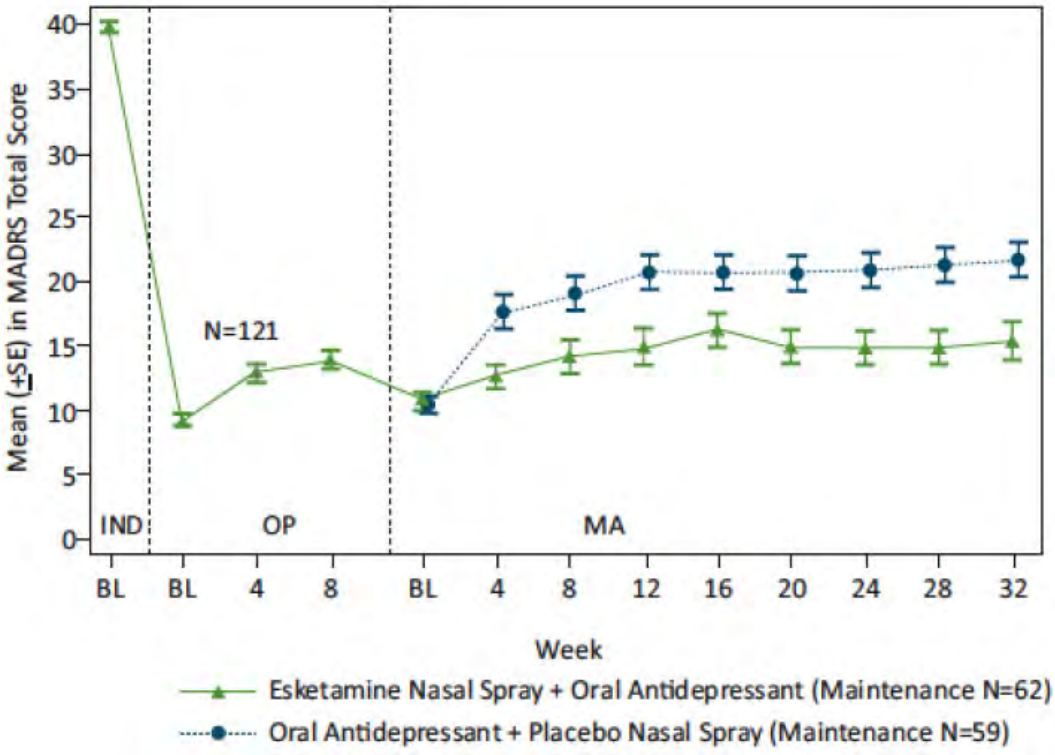


Figure 25b: Mean (± SE) in MADRS total score over time LOCF during the Induction, optimization and maintenance Phases in patients who were Stable Responders (88)



For stable remitters, both treatment groups showed an increase in mean MADRS total score from baseline (maintenance phase) to endpoint (maintenance phase). However, the mean (SD) increase was lower in subjects randomized to continue on ESK-NS (7.5 [11.59]) compared to subjects who discontinued ESK-NS (12.5 [13.63]). The LS mean (95% CI) difference between treatment groups was -5.2 (-8.77; -1.58), p<0.005. Similarly, among stable responders, the mean (SD) increase was 4.4 (11.38) in subjects randomized to continue ESK-NS + OAD compared to a mean (SD) increase of 11.4 (12.00) in subjects who were randomized to discontinue ESK-NS. The LS mean (95% CI) difference between treatment groups was -7.4 (-11.30; -3.55), p<0.001.

6.2 What is the clinically added value of esketamine in combination with SSRI or SNRI compared to placebo in combination with SSRI or SNRI for the treatment of adults with treatment resistant depression, assessed based on MSM in the current moderate to severe depressive episode.

6.2.1 Presentation of relevant studies

The clinical studies relevant for clinical question 2 are the three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3), the one maintenance study (SUSTAIN-1), and the long-term safety study (SUSTAIN-2). Furthermore, we deem that the safety data reported for all studies (inclusive SUSTAIN-3, SYNARPSE and the ATU study), under clinical question 1 is also relevant for clinical question 2.

6.2.2 Results per study

For clinical question 2 the Medicines Council has defined the population of interest to be patients over 18 years of age with moderate to severe treatment-resistant depression determined as patients who have not responded to two different types of antidepressants given in sufficient dose and for a sufficient length of time (≥ 4 weeks), or who have had depression for two or more years (same episode) regardless of which treatment and which has a MSM score of 9 or above. However, in addition to the subpopulation with a MSM ≥ 9 score, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. There are two main reasons for the inclusion of subpopulation with a MSM ≥ 7 score or MSM ≥ 8 score.
As stated in the Medcines Councils protocol for the evaluation of Spravato the MSM is developed to define treatment resistance in unipolar depression and is considered to have more stricter criteria than ICD-10, where it is even possible to classify the degree of difficulty treatment-resistant depression. The maximum score for MSM is 15 and the score is categorized into mild: 3-6, moderate: 7-10 and severe 11-15. Consequently, the first reason to include the subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is that they fall under the same MSM category "moderate" as the subpopulation with a MSM ≥ 9 score. The second reason for including the subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is that the clinical trial program of ESK-NS has not been powered to show results based on a population with a MSM ≥ 9 score. Consequently, the subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score are included as they are less strict in term of inclusion criteria and thus have a higher patient population than the subpopulation with MSM ≥ 9 score. For a comparison of the different MSM groups baseline characteristics in terms of components of the MSM score, see section 8.5.1.8

6.2.3 TRANSFORM-1

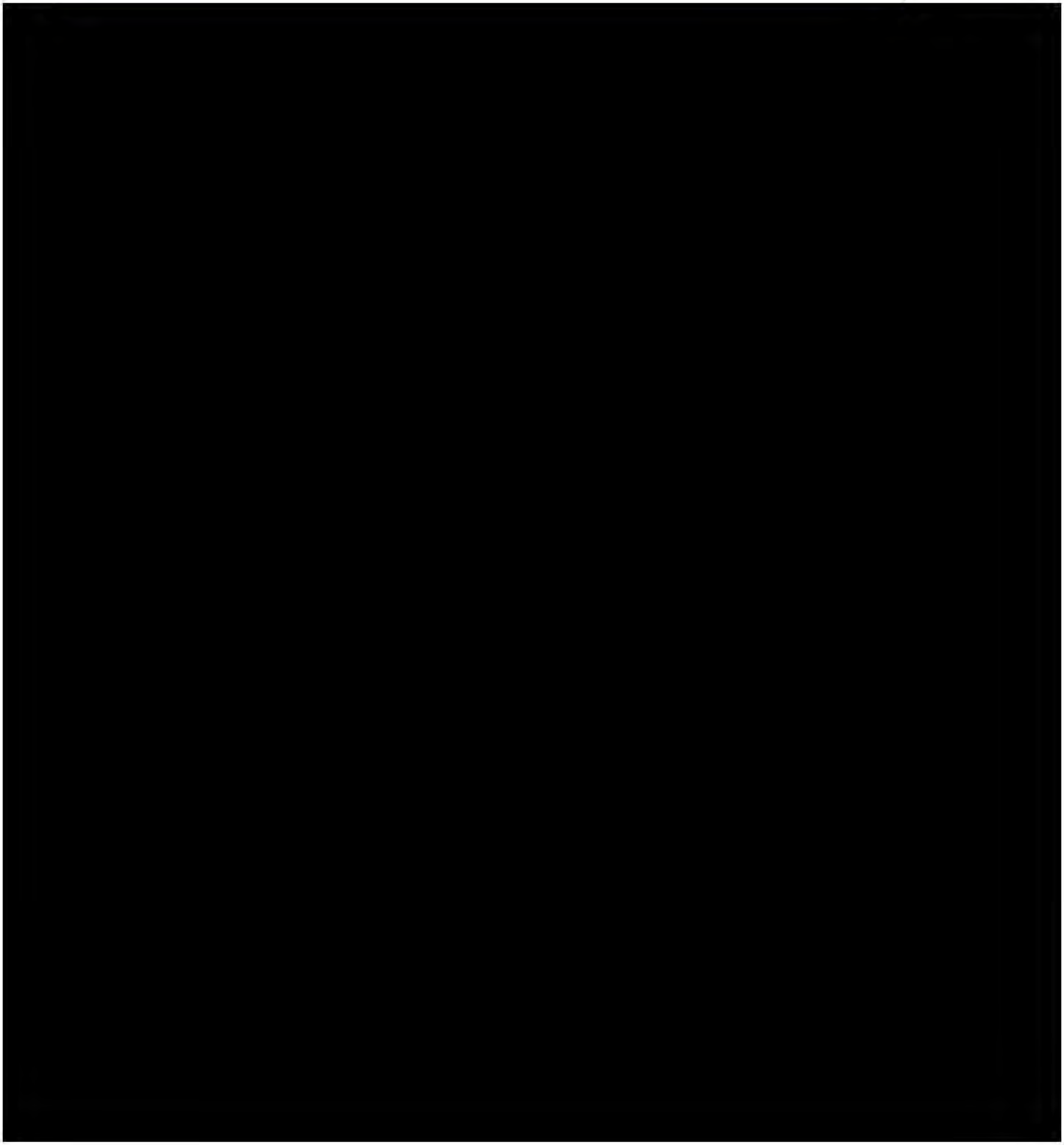
The results presented for TRANSFORM-1 are based on pooled analyses of the ESK-NS-84 mg and the ESK-NS-56 mg treatment arms. In addition to the subpopulation with a MSM ≥ 9 score which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for TRANSFORM-1 are summarized in table A3a of section 8.2 in the appendix.

MADRS total score

[redacted]

[redacted]

[redacted]

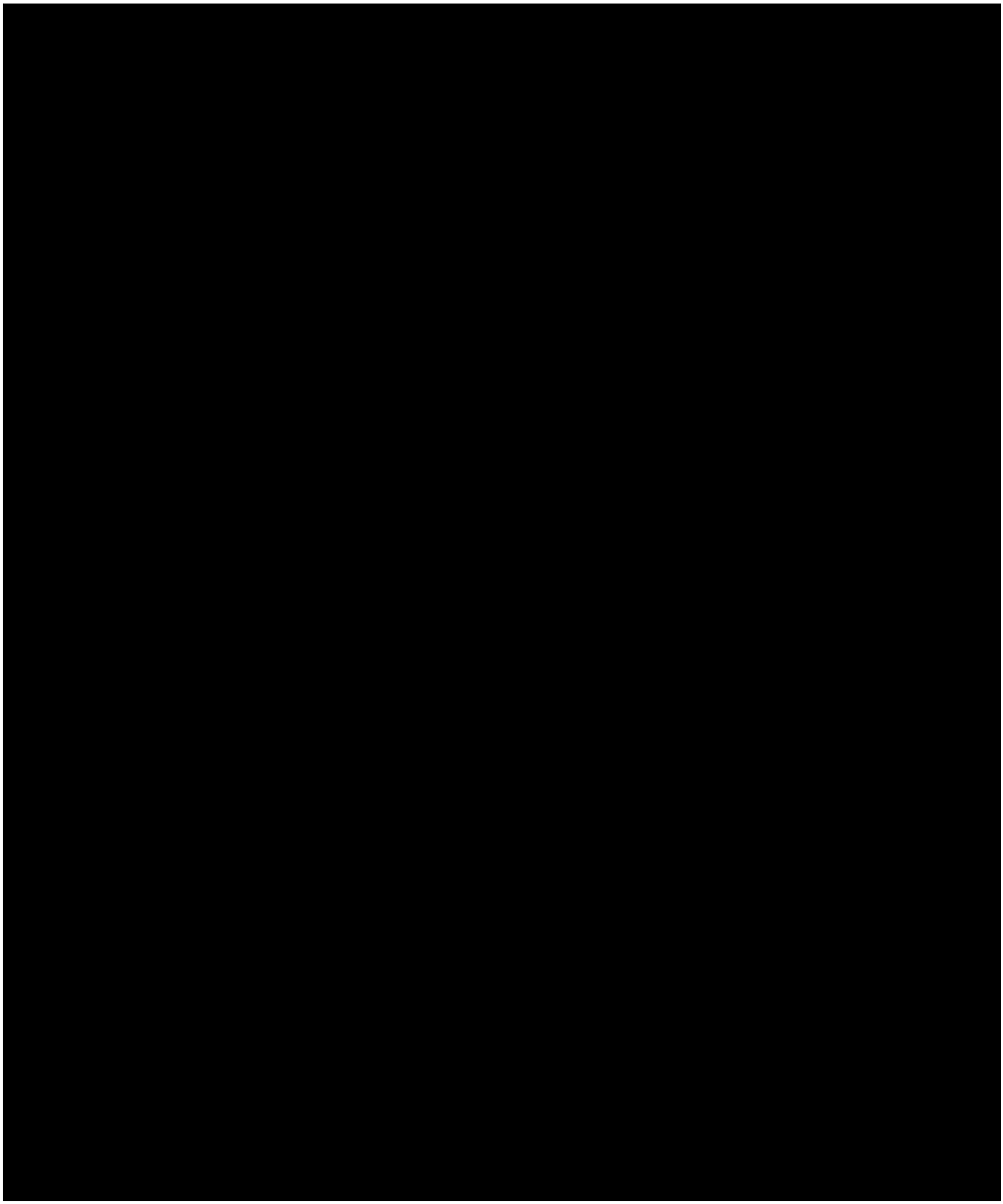


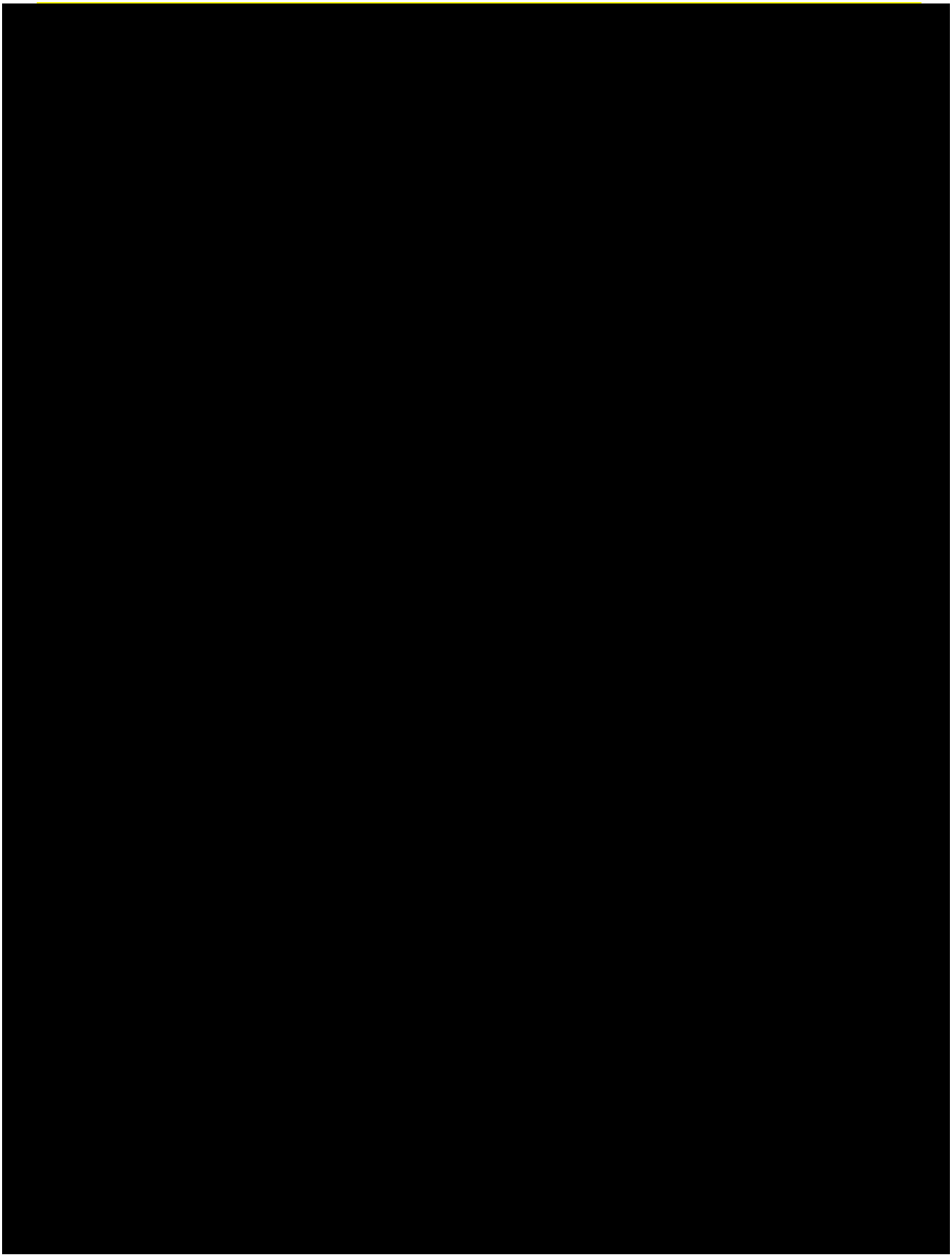
[redacted]

6.2.4 TRANSFORM-2

Following section presents results from TRANSFORM-2 for clinical question 2. In addition to the subpopulation with a MSM ≥ 9 score, which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for TRANSFORM-2 are summarized in table A3b of section 8.2 in the appendix.

[redacted]

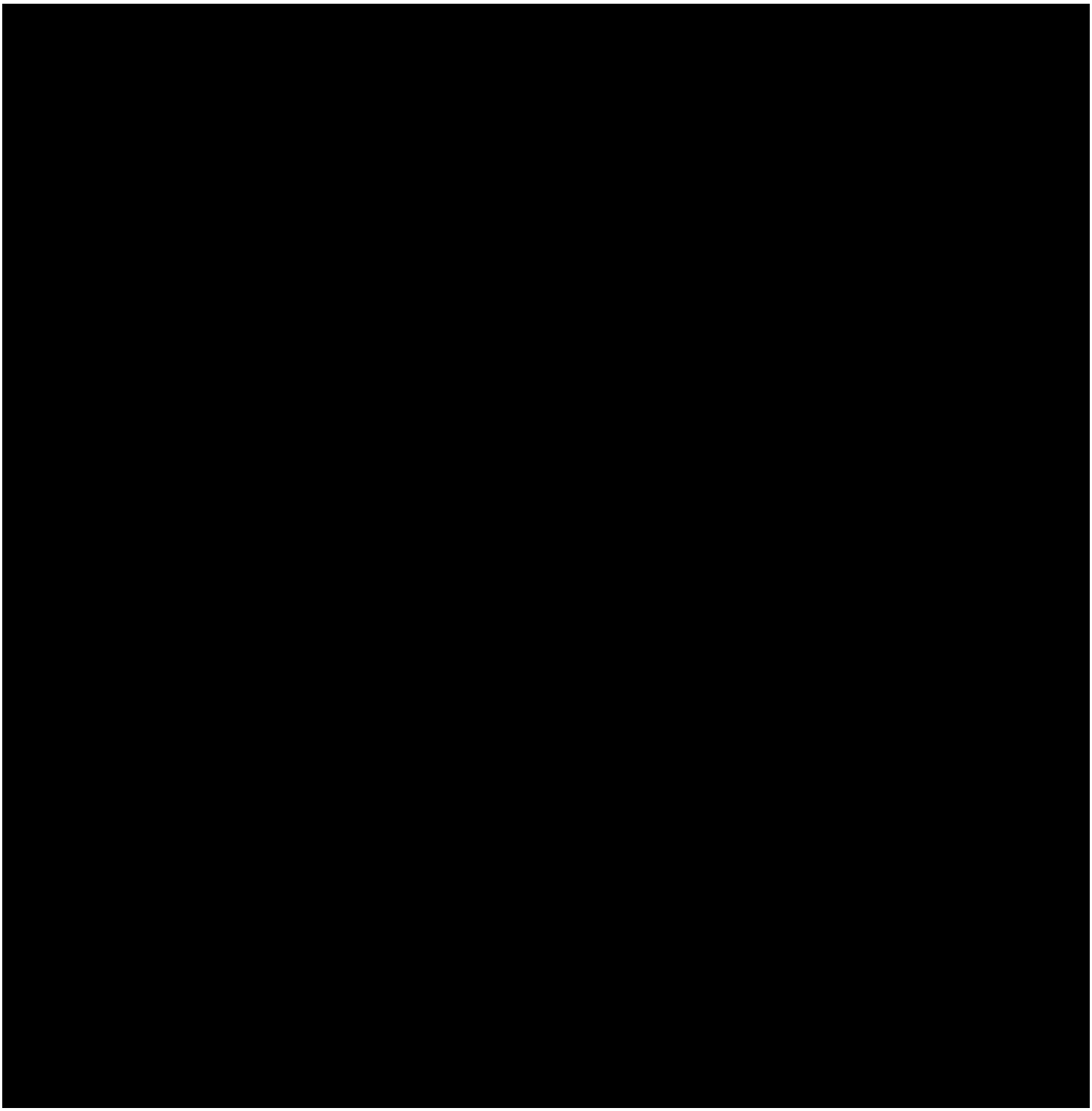




6.2.5 TRANSFORM-3

Following section presents results from TRANSFORM-3 for clinical question 2. In addition to the subpopulation with a MSM ≥ 9 score, which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for TRANSFORM-3 are summarized in table A3c of section 8.2 in the appendix.

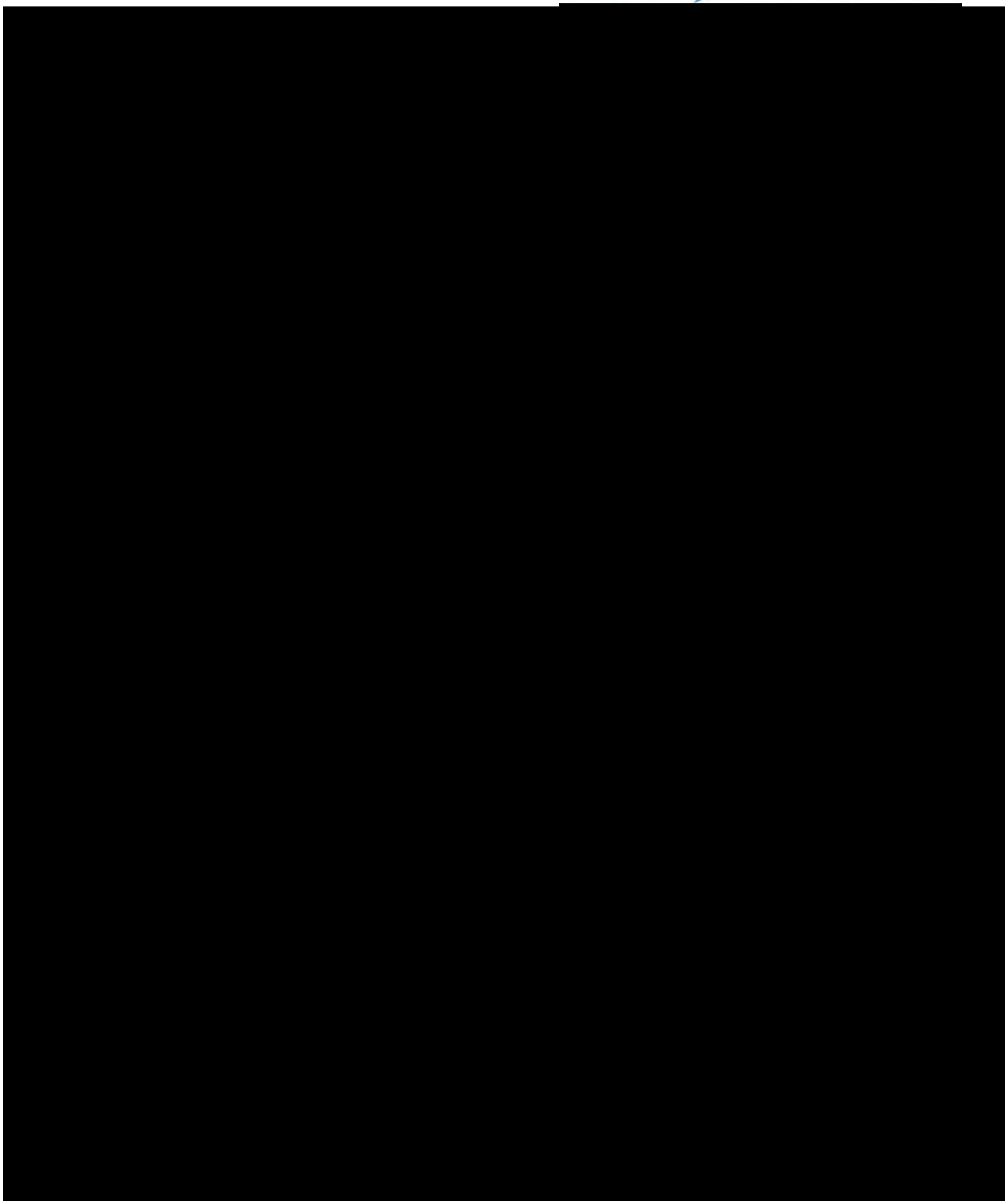
MADRS total score



[redacted]

Remission and Response

[redacted]



[redacted]

6.2.6 SUSTAIN-1

Following section presents results from SUSTAIN-1 for clinical question 2. In addition to the subpopulation with a MSM ≥ 9 score, which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for SUSTAIN-1 are summarized in table A3d of section 8.2 in the appendix. Separate safety data for the MSM subpopulation are not available and we therefore refer to the safety results presented for clinical question 1.

Serious adverse events

We refer to section 6.1.6 under clinical question 1, for the results on serious adverse events as reported for SUSTAIN-1.

Discontinuation due to adverse events

We refer to section 6.1.6 under clinical question 1, for the results on discontinuation due to adverse events as reported for SUSTAIN-1.

Narrative review of specific incidents, death for whatever reason and suicide attempts

We refer to section 6.1.6 under clinical question 1, for the narrative review of specific incidents, death for whatever reason and suicide attempts as reported for SUSTAIN-1. See also section 5.1.7 for a narrative review of specific incidents, death for whatever reason and suicide attempts covering all trials.

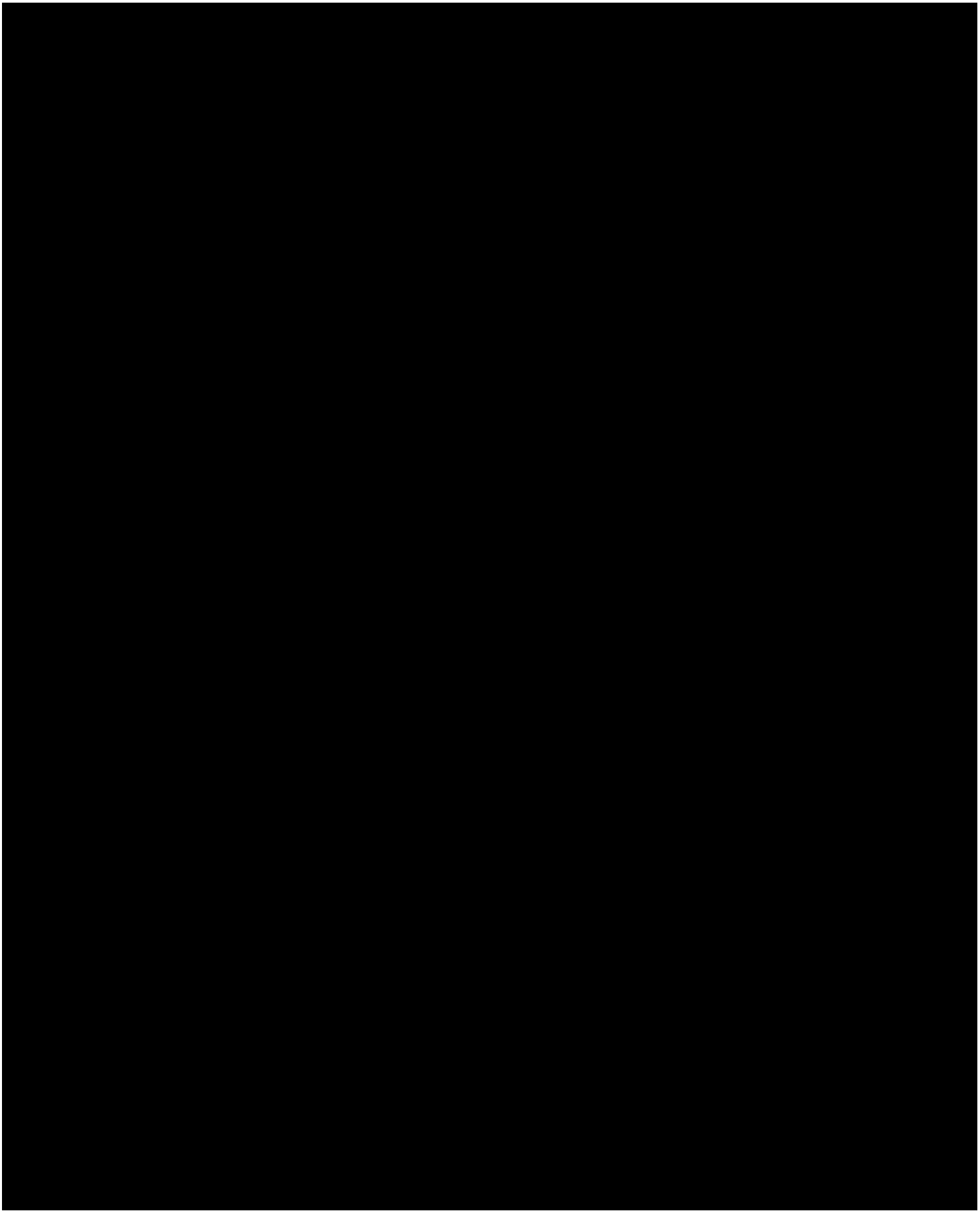
Quality of life

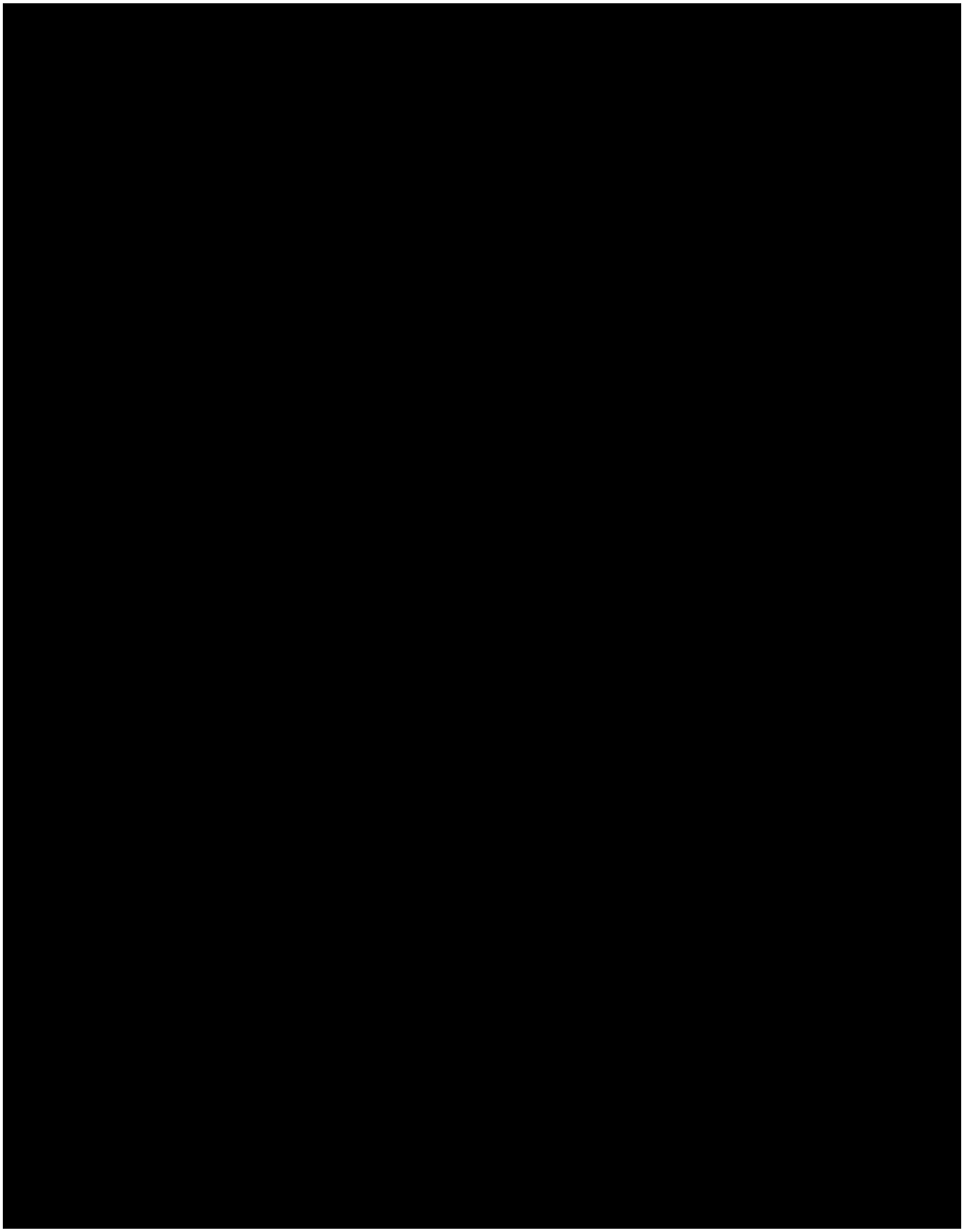
We refer to section 6.1.6 under clinical question 1, for the results on quality of life as reported for SUSTAIN-1.

Relapse in Stable Remitters

[redacted]

[redacted]





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6.2.7 SUSTAIN-2

Following section presents results from SUSTAIN-2 for clinical question 2. In addition to the subpopulation with a MSM ≥ 9 score, which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for SUSTAIN-2 are summarized in table A3e of section 8.2 in the appendix. Separate safety data for the MSM subpopulation are not available and we therefore refer to the safety results presented for clinical question 1.

Serious adverse events at induction

We refer to section 6.1.7 for the results on serious adverse events for clinical question 1 as well as the additional safety information reported for SUSTAIN-2 in section 6.1.7.

Serious adverse events at maintenance

We refer to section 6.1.7 for the results on serious adverse events at maintenance for clinical question 1 as well as the additional safety information reported for SUSTAIN-2 in section 6.1.7.

Discontinuation due to adverse events at induction

We refer to section 6.1.7 for the results on discontinuation due to adverse events at induction for clinical question 1 as well as the additional discontinuation information reported for SUSTAIN-2 in section 6.1.7.

Discontinuation due to adverse events at maintenance

We refer to section 6.1.7 for the results on discontinuation due to adverse events at maintenance for clinical question 1 as well as the additional discontinuation information reported for SUSTAIN-2 in section 6.1.7.

Quality of life

We refer to section 6.1.7 for the SUSTAIN-2 results on change from baseline in mean (SD) EQ-5D-5L Health Status Index (HSI) score to end of optimization/maintenance for clinical question 1.

6.2.8 TRD cohort study

Following section presents results from the TRD cohort study for clinical question 2. In addition to the subpopulation with a MSM ≥ 9 score, which is equal to clinical question 2 defined by the Medicines Council, results on subpopulations with a MSM ≥ 7 score or MSM ≥ 8 score is also presented. The results for the TRD cohort study are summarized in table A3i of section 8.2 in the appendix. Separate safety data for the MSM subpopulation are not available and we therefore refer to the safety results presented for clinical question 1.

MADRS total score at 6 months

Serious adverse events at induction

We refer to section 6.1.11 for the results on serious adverse events for clinical question 1 as well as the additional safety information reported for the TRD cohort in section 6.1.11.

Serious adverse events at maintenance

We refer to section 6.1.11 for the results on serious adverse events at maintenance for clinical question 1 as well as the additional safety information reported for the TRD cohort in section 6.1.11.

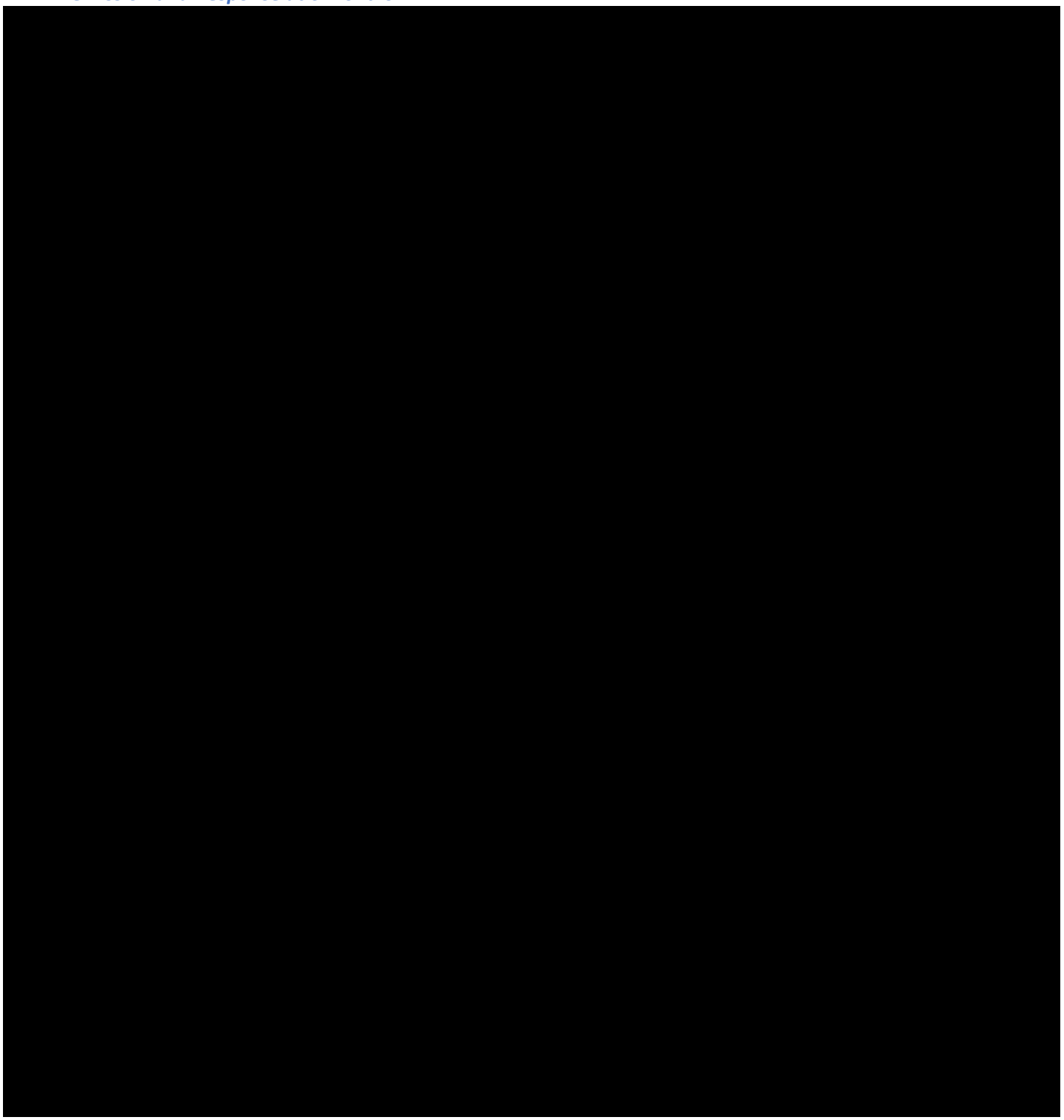
Discontinuation due to adverse events at induction

We refer to section 6.1.11 for the results on discontinuation due to adverse events at induction for clinical question 1 as well as the additional discontinuation information reported for the TRD cohort in section 6.1.11.

Discontinuation due to adverse events at maintenance

We refer to section 6.1.11 for the results on discontinuation due to adverse events at maintenance for clinical question 1 as well as the additional discontinuation information reported for the TRD cohort in section 6.1.11.

Remission and Response at 6 months



[redacted]

Quality of life

We refer to section 6.1.11 for the TRD cohort results on change from baseline in mean (SD) EQ-5D-5L Health Status Index (HSI) score or clinical question 1.

6.2.9 Comparative analyses

For the comparative analyses of the subgroups with a MSM score of MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9, the three acute, 4-week treatment studies (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3) comparing of ESK-NS + OAD directly with OAD + NS-PBO has been utilized As per the Handbook of the Medicines Council's process and methodologies for new pharmaceuticals and indication expansions version 2.4, a meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model. (72)

Forest plots available in section 8.4 show the risk ratio and mean difference results of the performed meta-analyses. All the I^2 statistic were 0% for the MSM ≥ 7 and MSM ≥ 8 subpopulations and chi-squared test were non-significant, thus the tests for heterogeneity does not indicate presence of heterogeneity (73). Consequently, the meta-analyses are all based on fixed effects estimates. However, for the MSM ≥ 9 subpopulation the I^2 statistic were above 50%. Consequently, the meta-analyses were based on random effects estimates.

The absolute differences in effect were calculated using the estimated risk ratio (RR) from the meta-analyses as well as the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. (74)

For the long-term treatment efficacy, the long-term safety study SUSTAIN-2 and the TRD cohort study has been utilized to conduct an indirect treatment comparison. Detailed information regarding the methodology and the results are available in appendix 8.5, whereas the main results and conclusion are presented in this section.

The comparative results for clinical question 2 are summarized in table A4.1 of section 8.2 in the appendix

The Phase 2 study, SYNAPSE was not included in the meta-analyses of the short-term studies and neither is comparative results from SYNAPSE presented in this section. This is due to SYNAPSE investigating esketamine nasal spray (as add-on to continued OAD) for the treatment of patients with moderate to severe MDD who failed to respond to at least 2 AD therapies during their current MDD episode (History of inadequate response to ≥2 ADs of which ≥1 AD was used in the current episode of depression). It should be noted that this inclusion criteria differs from the TRD definition as well as the populations studied in the Phase III trials. Furthermore, as participants in the SYNAPSE study continued their existing OAD treatment during the study, the intervention and comparator is not in line with the intervention and comparator in the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 as patient in the phase 3 trials initiated a new OAD in combination with either ESK-NS or PBO-NS.
However, the results from the SYNAPSE study are presented in section 6.1.9 as the Scientific Committee has expressed interest in the results of SYNAPSE and to underline and support the efficacy and safety of Spravato observed in the TRANSFORM studies.

MADRS total score at 6 months

Operationalisation of change in depressive symptoms measured according to MADRS total score and justification for the final estimation

Same as for the full TRD population (clinical question 1), thus we refer to the description in section 6.1.13. However, only difference is that the analyses of remission under this section is done for the subpopulation of patients with a MSM ≥ 7 score, MSM ≥ 8 score or MSM ≥ 9 score.

Results for the ITC of SUSTAIN-2 and TRD cohort study

[redacted]

Serious adverse events at induction

We refer to section 6.1.13 for the comparative analyses done on serious adverse events at induction for clinical question 1 as well as the additional safety information reported for SUSTAIN-2 and SUSTAIN-3 in section 6.1.7 and 6.1.8, respectively.

Serious adverse events at maintenance

We refer to section 6.1.13 for the comparative analyses done on serious adverse events at maintenance for clinical question 1 as well as the additional safety information reported for SUSTAIN-2 and SUSTAIN-3 in section 6.1.7 and 6.1.8, respectively.

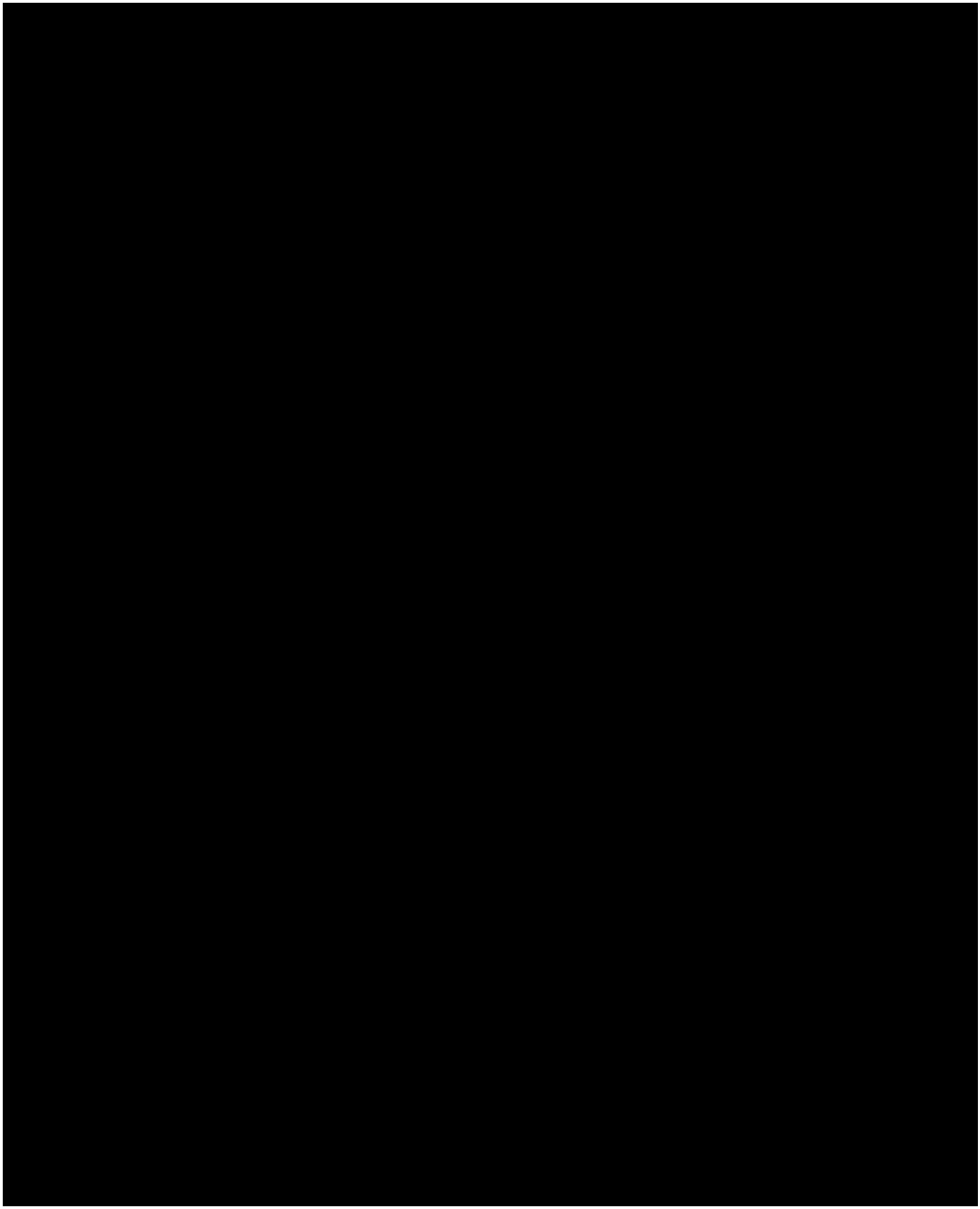
Discontinuation due to adverse events at induction

We refer to section 6.1.13 for the comparative analyses done on discontinuation due to adverse events at induction for clinical question 1 as well as the additional discontinuation information reported for SUSTAIN-2 and SUSTAIN-3 in section 6.1.7 and 6.1.8, respectively.

Discontinuation due to adverse events at maintenance

We refer to section 6.1.13 for the comparative analyses done on discontinuation due to adverse events at maintenance for clinical question 1 as well as the additional discontinuation information reported for SUSTAIN-2 and SUSTAIN-3 in section 6.1.7 and 6.1.8, respectively.

Remission at induction



[redacted]

Remission at induction based solely on TRANSFORM-2

A comparative analysis between ESK-NS + OAD and OAD + PBO-NS for patient with MSM ≥ 9 based solely on TRANSFORM-2 is presented in the following, to show the efficacy of ESK-NS in a population aged 18-64 utilizing the label flexible dosing of ESK-NS. Consequently, the analyses exclude the TRANSFORM-1 study evaluating fixed dose ESK-NS-56mg or -84mg + OAD (which does not correspond with the label) versus a newly initiated OAD + PBO-NS for the treatment of TRD in adults aged 18–64 years. Furthermore, the patients aged ≥65 are excluded as efficacy of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD was investigated in TRANSFORM-3

Conclusively, the analyses based only on TRANSFORM-2 consists of a TRD patient population with an age of 18-64 that reflects the labelled flexibly dose of ESK-NS + OAD which the Scientific Committee and the Medicines Council can take into consideration.

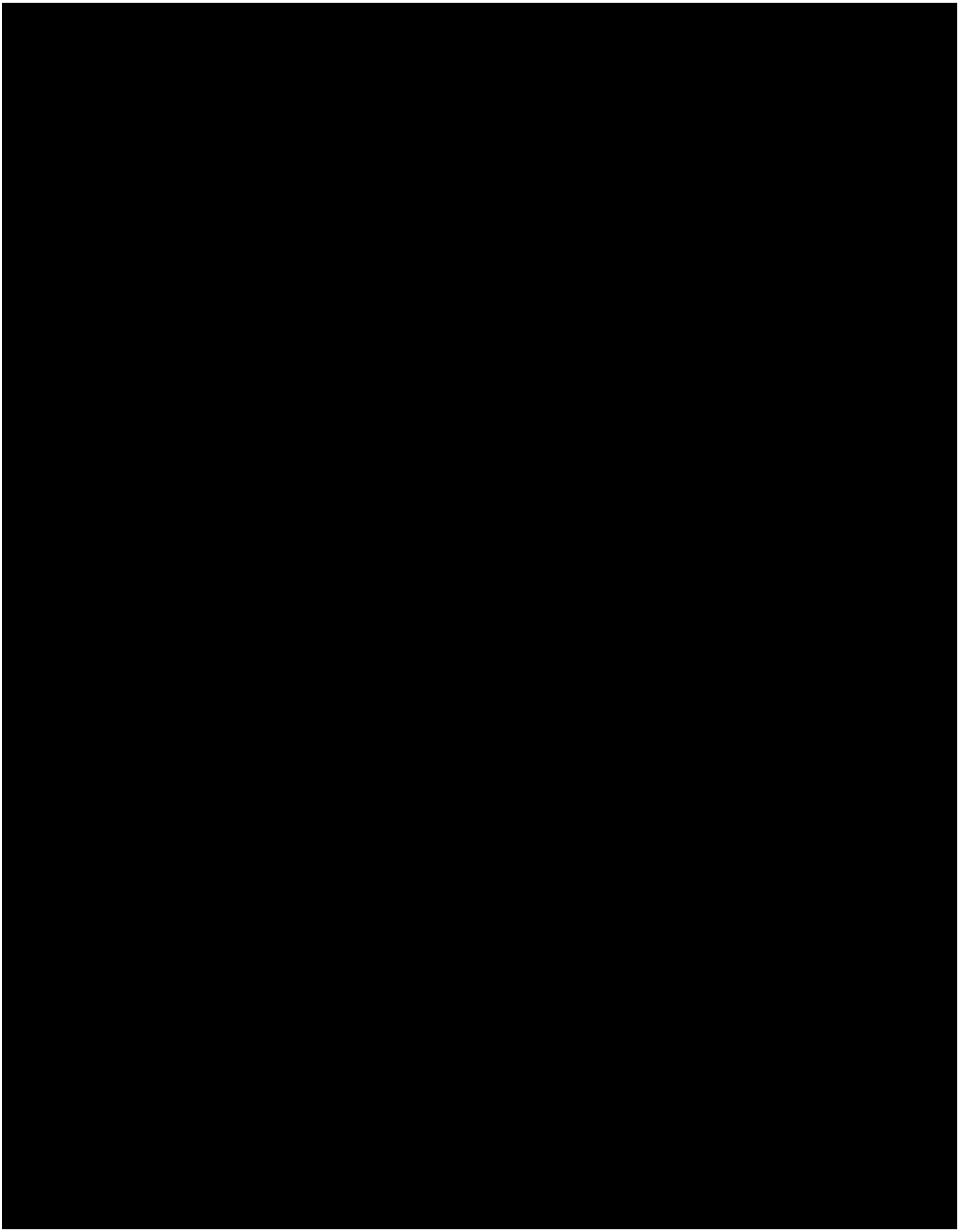
[redacted]

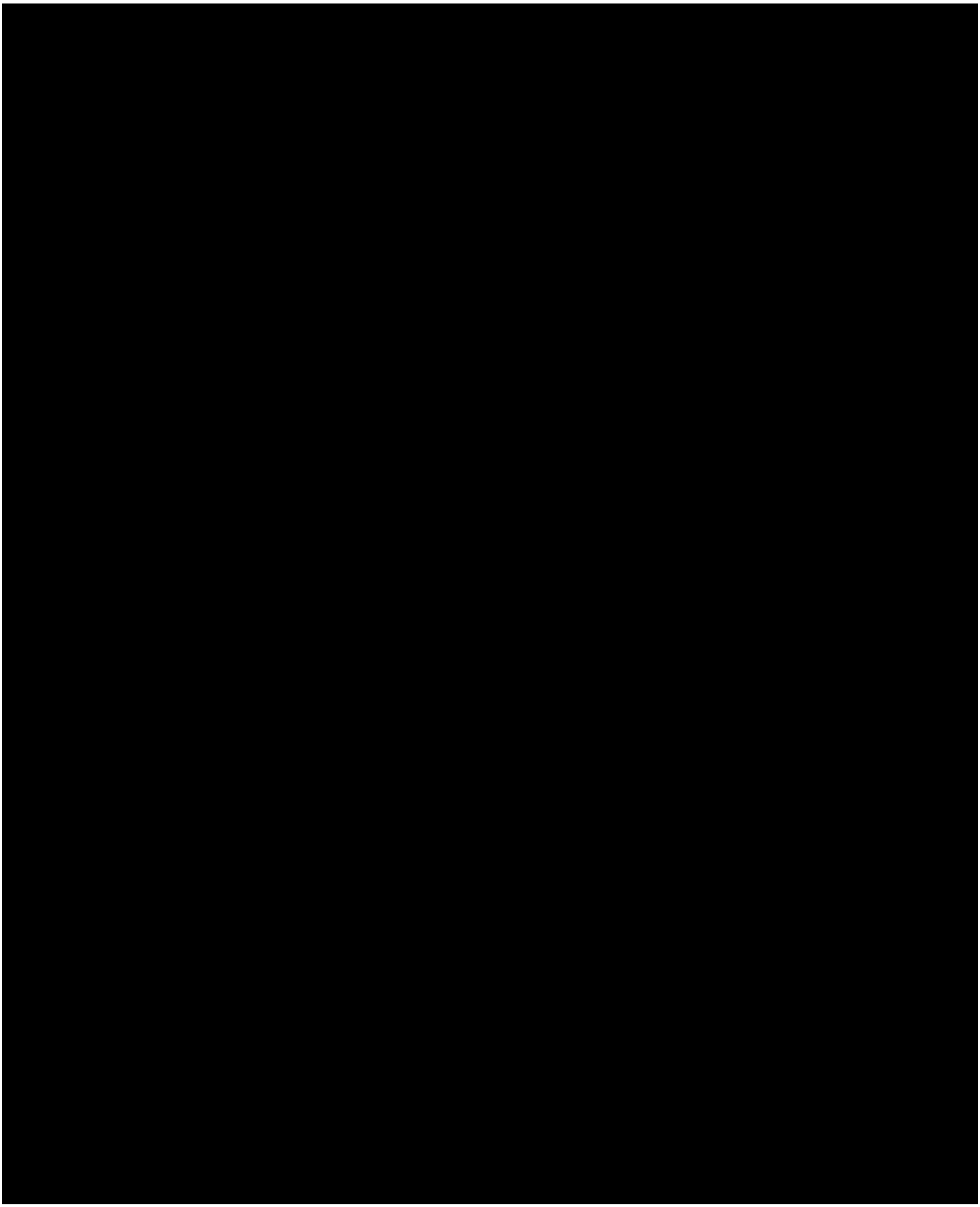
Remission at 6 months for the MSM ≥ 7 subpopulation – ITC of SUSTAIN-2 and the TRD cohort study.

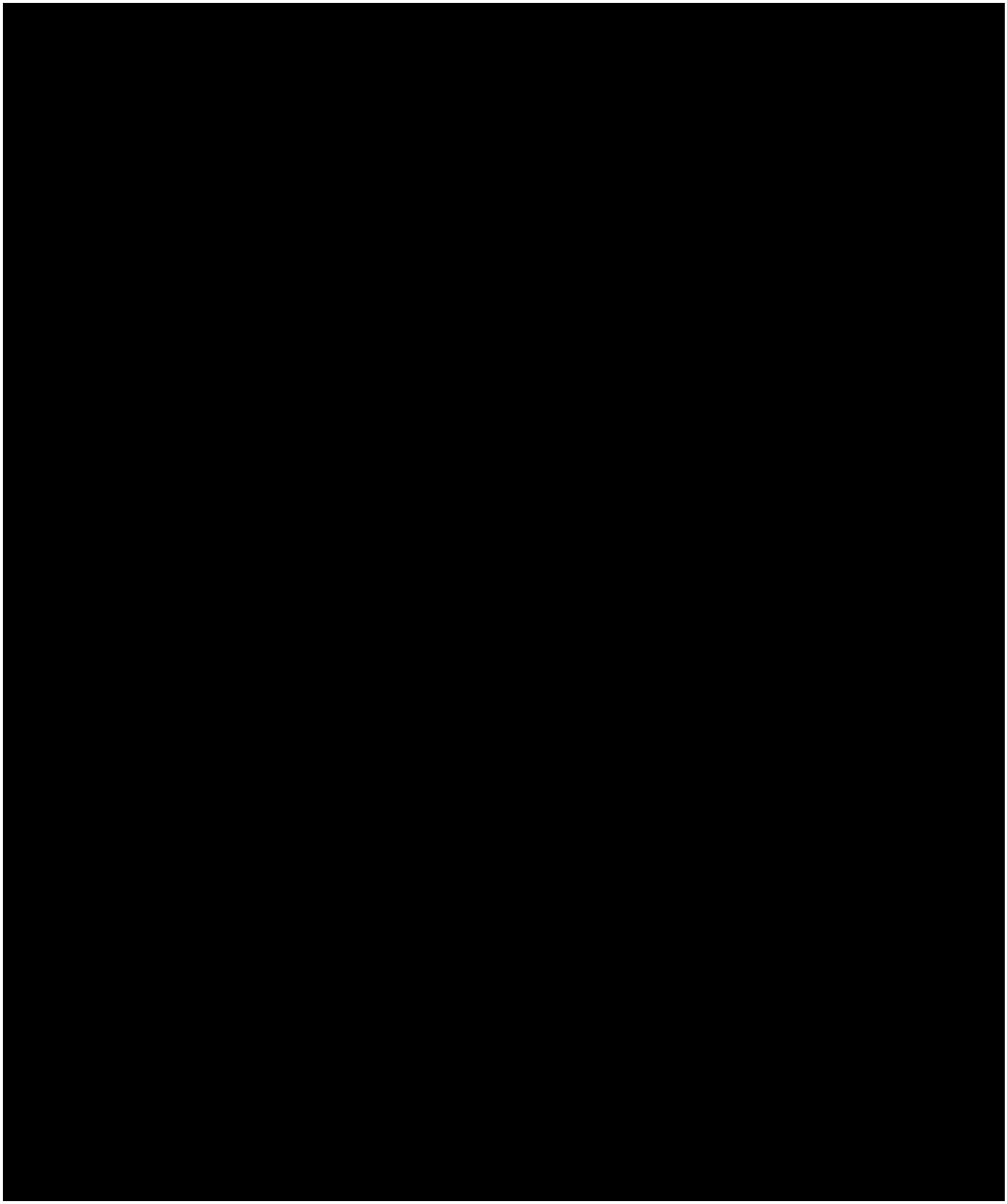
Operationalisation of the remission and justification for the final estimation

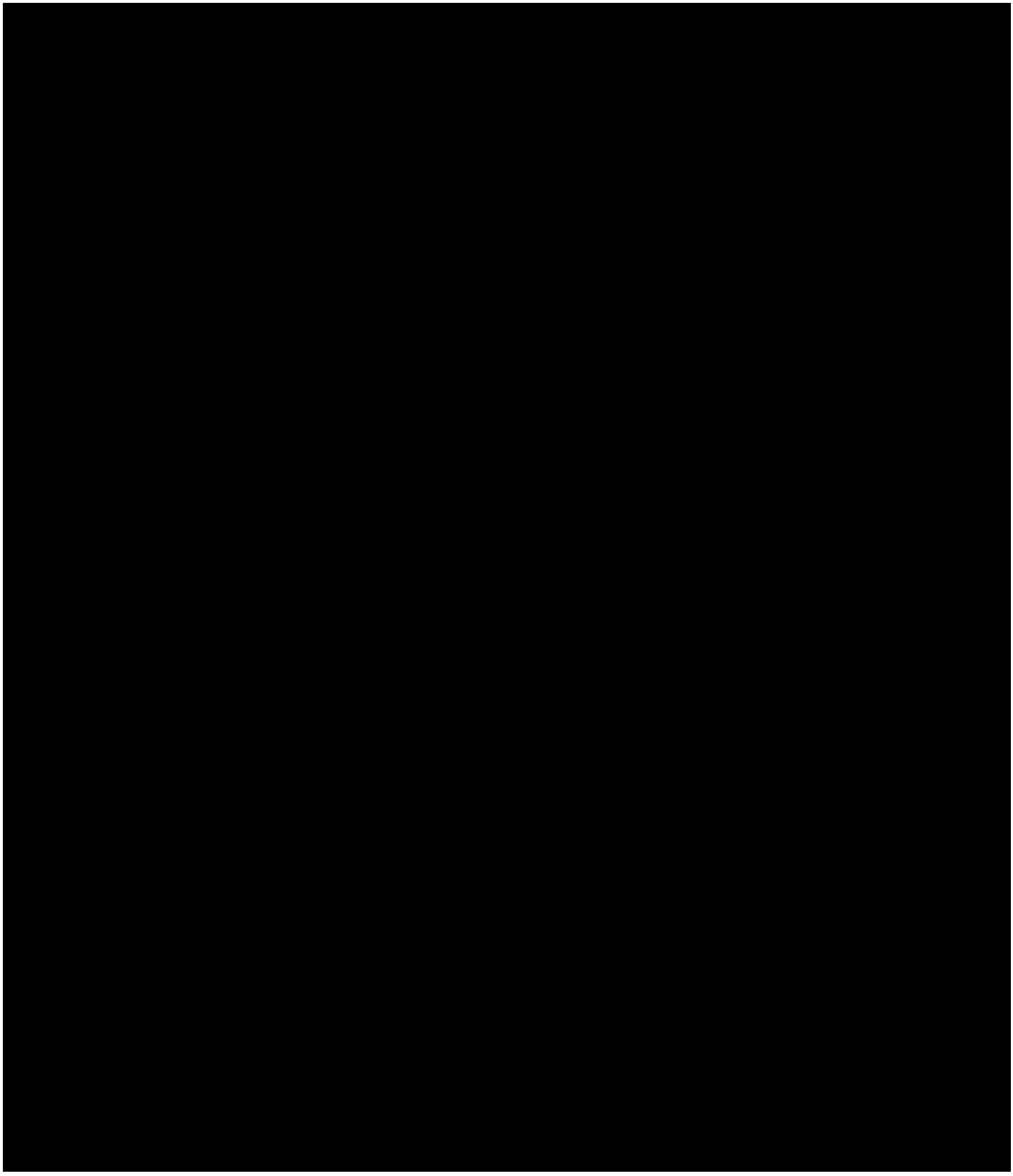
Same as for the full TRD population (clinical question 1), thus we refer to the description in section 6.1.13. However, only difference is that the analyses of remission under this section is done for the subpopulation of patients with a MSM ≥ 7 score.

Results for the ITC of SUSTAIN-2 and TRD cohort study MSM ≥ 7







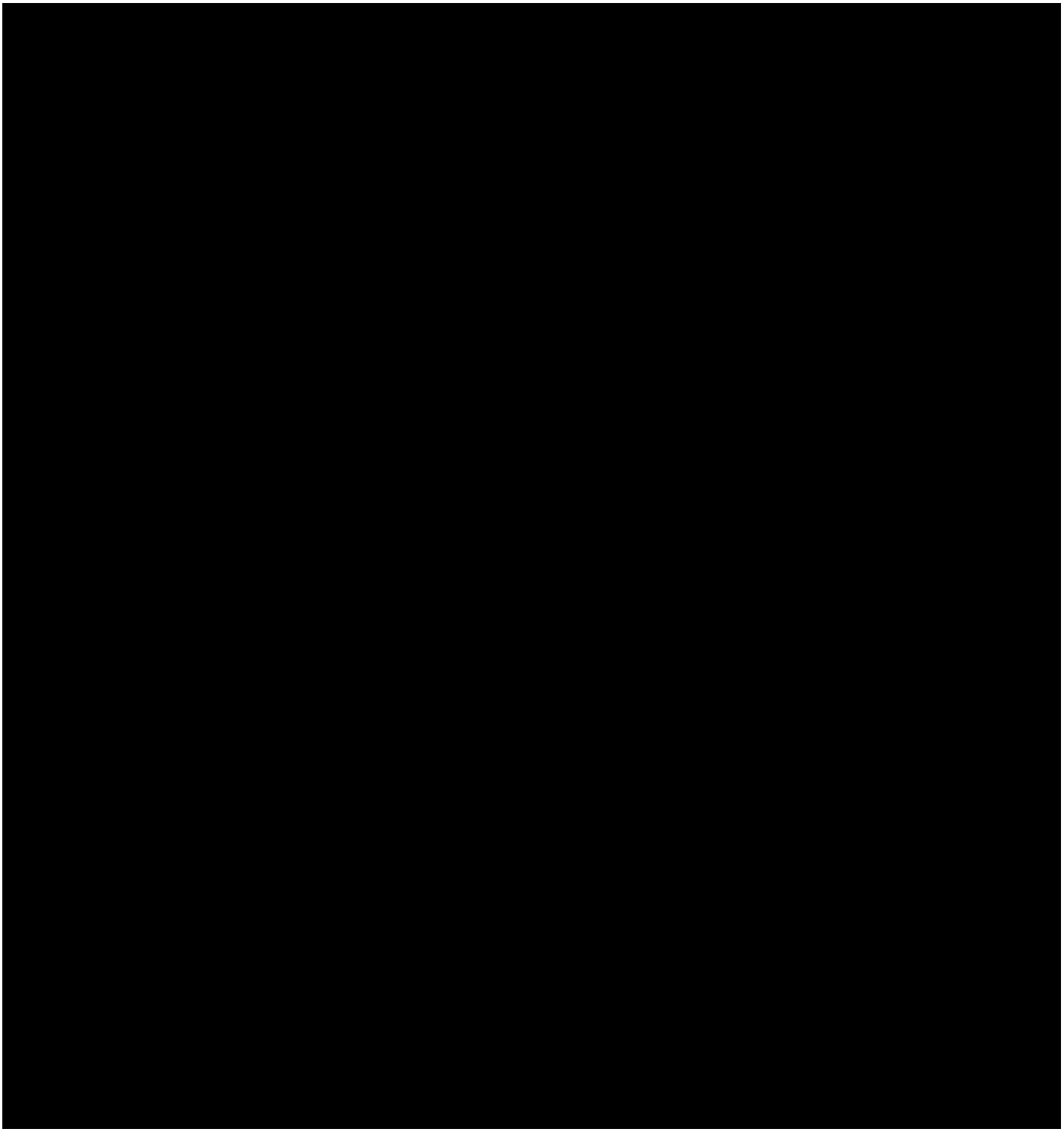


[redacted]

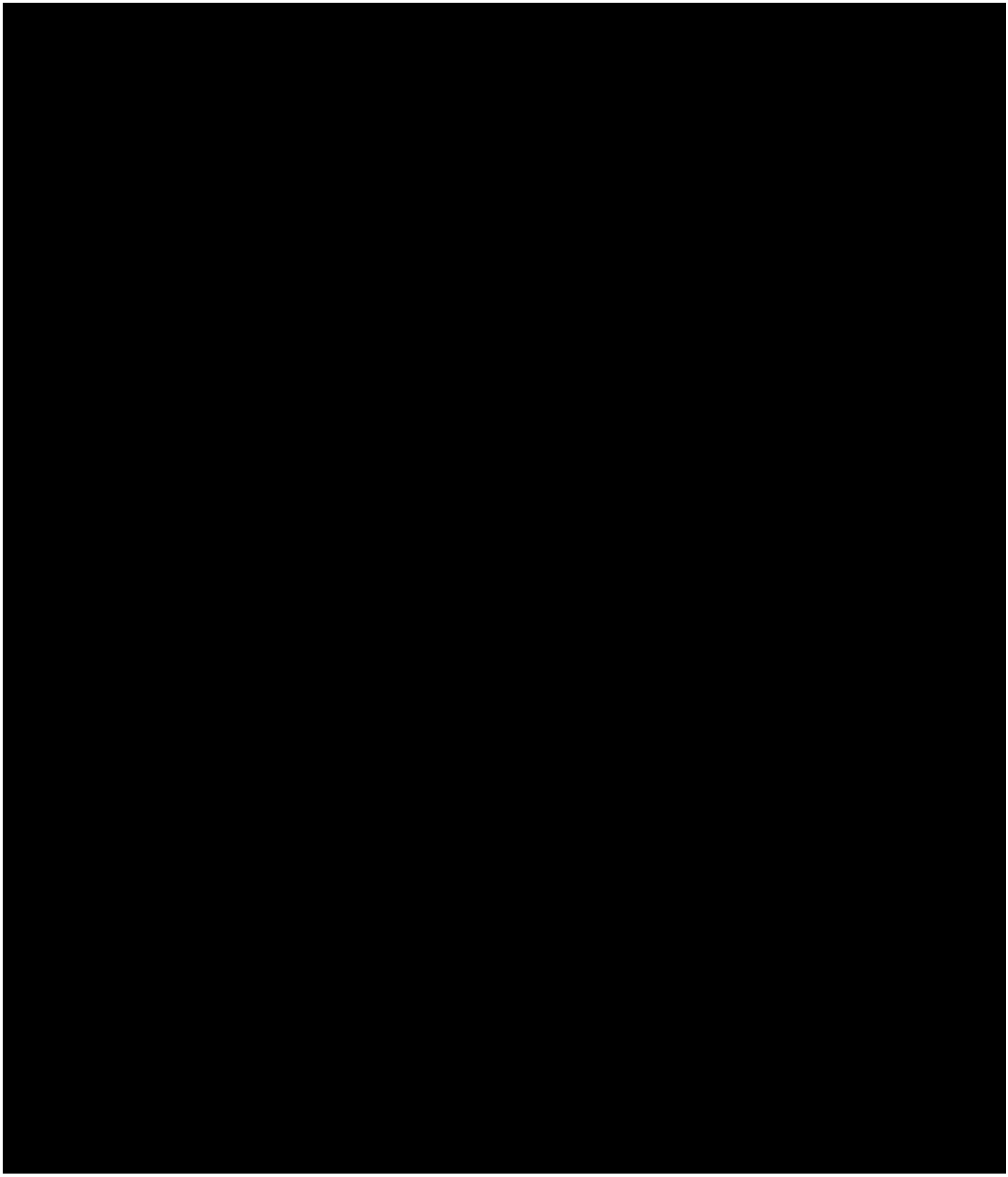
Response at induction based solely on TRANSFORM-2

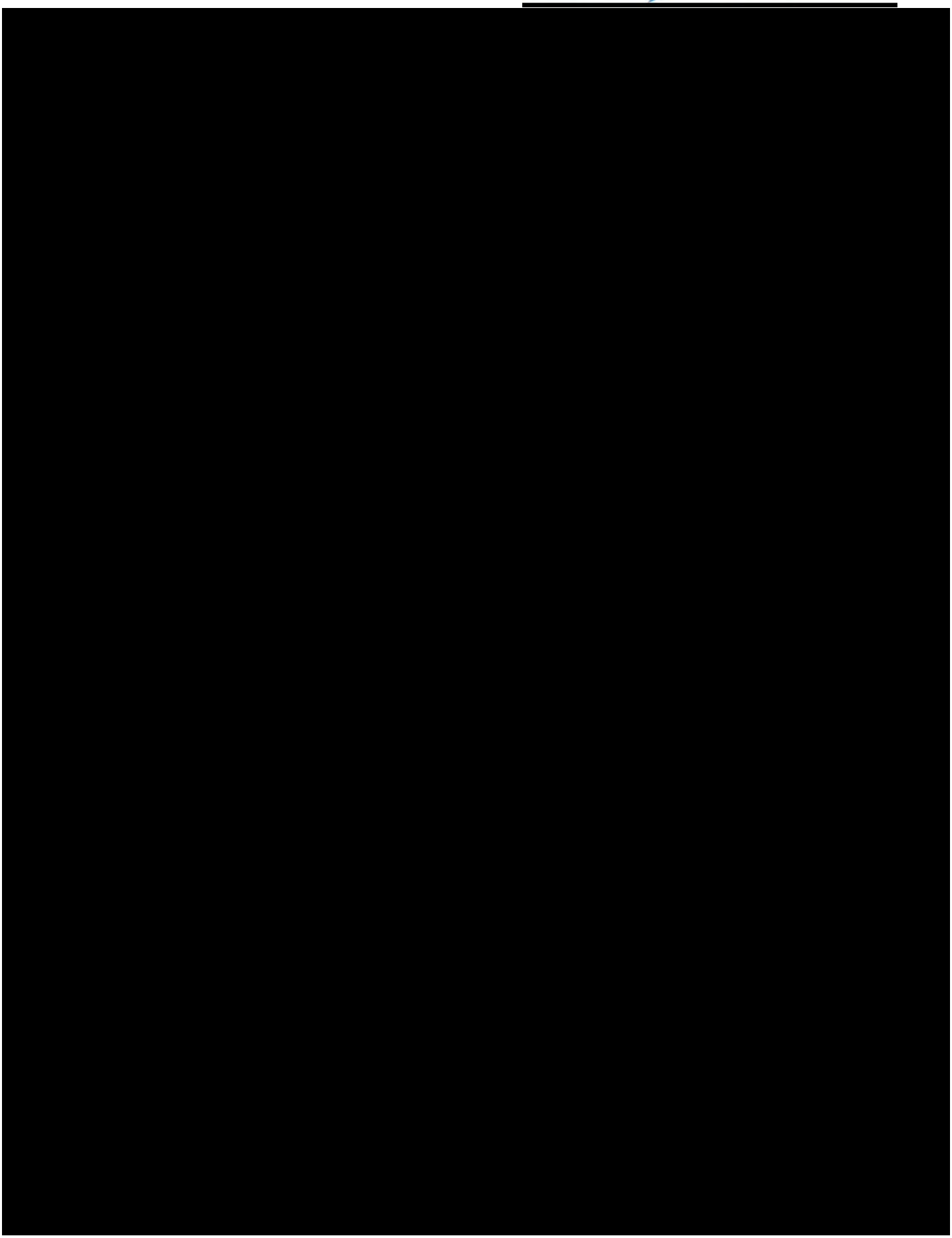
A comparative analysis between ESK-NS + OAD and OAD + PBO-NS based solely on TRANSFORM-2 is presented in the following, to show the efficacy of ESK-NS in a population aged 18-64 utilizing the labelled flexible dosing of ESK-NS. Consequently, the analyses exclude the TRANSFORM-1 study evaluating fixed dose ESK-NS-56mg or -84mg + OAD (which does not correspond with the label) versus a newly initiated OAD + PBO-NS for the treatment of TRD in adults aged 18–64 years. Furthermore, the patients aged ≥65 are excluded as efficacy of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD was investigated in TRANSFORM-3

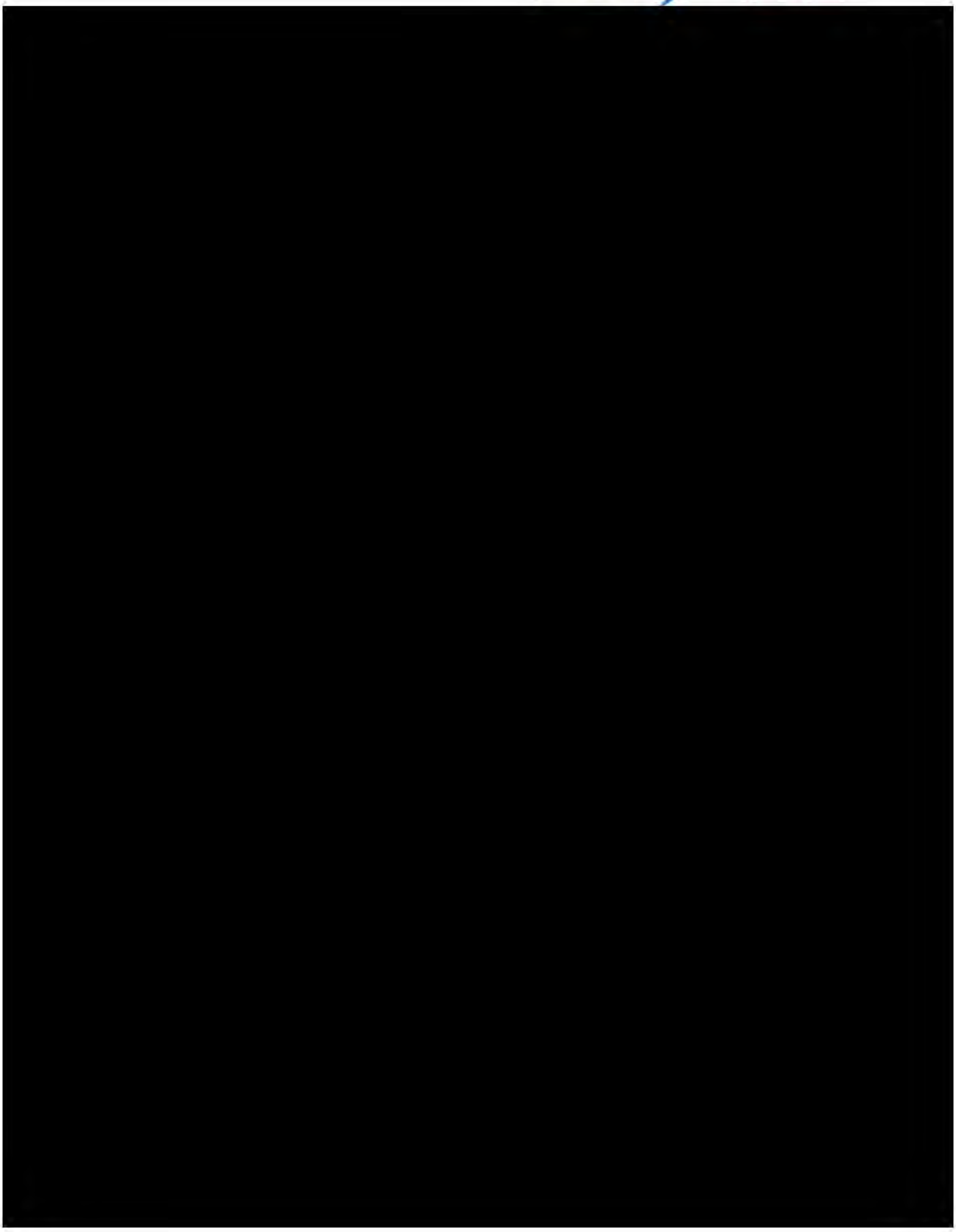
Conclusively, the analyses base only on TRANSFORM-2 consists of a more restricted population that reflects the labelled flexibly dose of ESK-NS + OAD which the Scientific Committee and the Medicines Council can take into consideration.

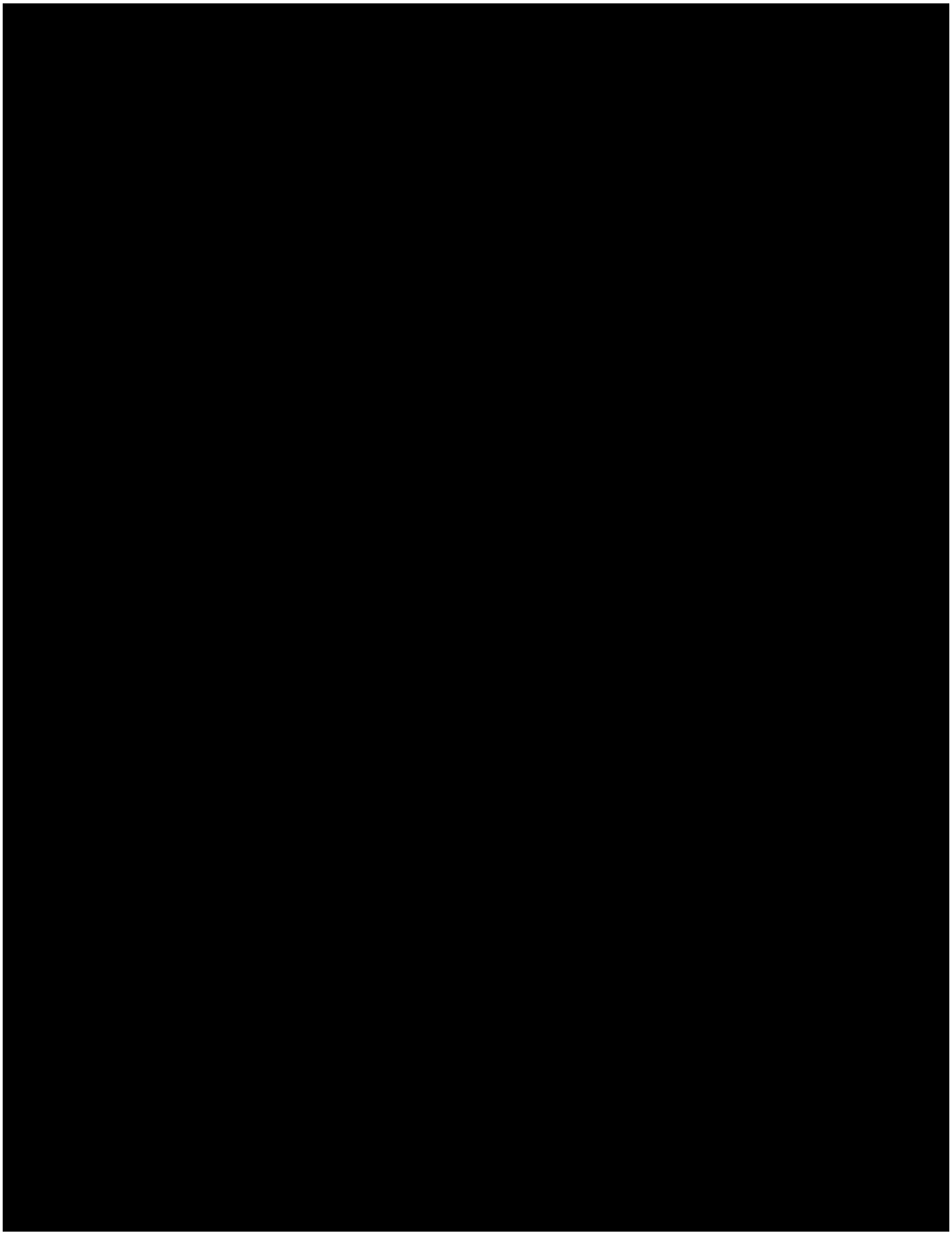


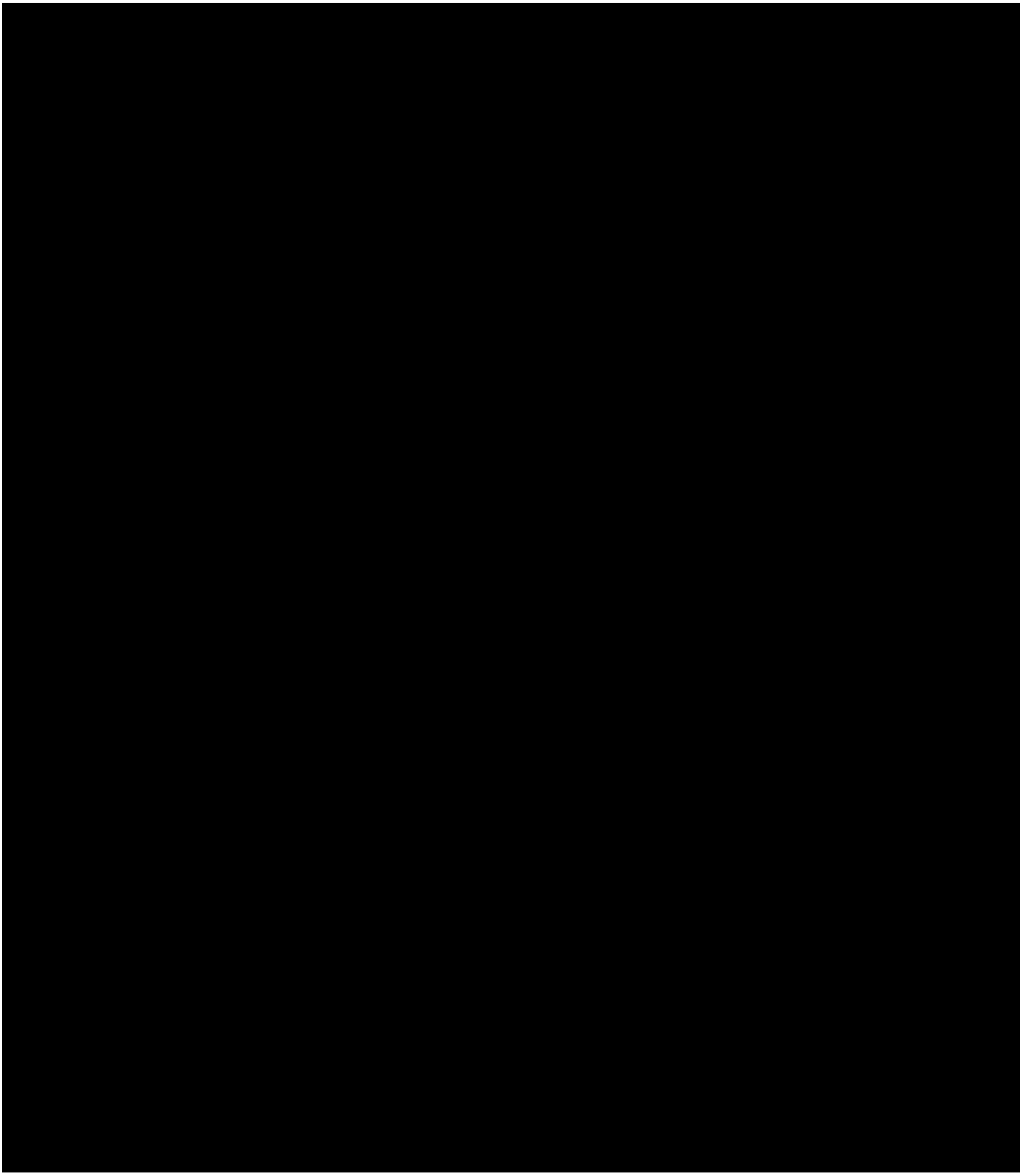
Response at 6 months for the MSM ≥ 7 subpopulation – ITC of SUSTAIN-2 and the TRD cohort study.











Quality of life at maintenance

We refer to section 6.1.13 for the comparative analyses done on quality of life at maintenance for clinical question 1.

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8 Appendices

Main characteristics of included studies

8.1 Study characteristics

Table A2 Main study characteristics of TRANSFORM-1 (19, 20)

Trial name	TRANSFORM-1
NCT number	NCT02417064
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching adult subjects (18-64 years) with TRD from a prior antidepressant treatment (to which they have not responded) to either fixed doses of ESK-NS (56 mg or 84 mg) + a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS
Publications – title, author, journal, year	Efficacy and Safety of fixed-dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1), Fedgchin et al., Int J Neuropsychopharmacol, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with moderate to severe TRD (nonresponse to ≥1 to ≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of fixed doses of ESk-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator; escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS 56 mg, ESK-NS 84 mg or PBO-NS. Randomization was balanced by using randomly permuted blocks (blocks size of 6) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. The same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of esketamine nasal spray (56 mg/84 mg) or treatment (esketamine or placebo) they were taking. The study consists of 3 phases: 1. Screening/Prospective Observational Phase: 4 Weeks + optional antidepressant taper period ≤3 weeks 2. Double-blind Induction Phase 4-weeks 3. Post-treatment follow-up Phase: 24-weeks (only for those participants ineligible or unwilling to participate in subsequent long-term study SUSTAIN-1 following double-blind induction phase. Thus, eligible participants rollover into a SUSTAIN-1 and was not part of the Follow-up Phase)

Follow-up time	**Double-blind induction phase (4 weeks)** Of the 346 subjects randomly assigned to treatment, 315 (91%) subjects completed the 28-day double-blind induction phase, and 31 (9%) subjects were withdrawn **Follow-up phase (24 weeks)** 168 subjects entered the follow-up phase, 36 (21.4%) of these subjects completed the follow-up phase and 132 (78.6%) of these subjects were withdrawn from the follow-up phase (19) **Maintenance study enrollment (SUSTAIN-1)** 150 subjects continued into the SUSTAIN-1 maintenance of effect study (only responders defined as ≥50% reduction in the MADRS total score from baseline to the end of the 4-week double-blind induction phase were eligible).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive • At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participants must have had non-response (less than or equal to [<=25] percent [%] improvement) to >=1 but less than or equal to (<=) 5 (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history and pharmacy/prescription records, for the current episode of depression. • Participant is taking a different oral antidepressant treatment on the MGH-ATRQ for at least the previous 2 weeks at or above the minimum therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (i.e, duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression

	• Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria
Intervention	**Double blind Induction phase (4 weeks)** Beginning from the double-blind induction phase, patients (n=346) were randomized 1:1:1 to receive: • ESK-NS 56 mg + OAD (n=117) • ESK-NS 84 mg + OAD (n=116) • Active comparator: OAD + PBO-NS (n=113)
Baseline characteristics	*See table A2a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28). **Secondary endpoints** The key secondary endpoints assessed: • The proportion of participants with onset of clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind phase with 1 excursion (i.e., ≥25% reduction relative to baseline MADRS allowed on days 8, 15 or 22) • Change from baseline in SDS total score to end of double-blind induction phase • Change from baseline in PHQ-9 total score to end of double-blind induction phase
Method of analysis	**Sample Size, power calculation** The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and OAD + PBO-NS arms, a SD of 12 , a 2-sided significance level of 0.025, and a drop-out rate of 25%. 116 patients were required to be randomized to each treatment group to achieve 90% power using a fixed design assuming no interim analysis. **Efficacy analyses**

	Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase) using a truncated fixed sequence parallel gatekeeping procedure to adjust for multiplicity and to strongly control type I error. For each endpoint, testing of the ESK-NS 56 mg dose group was conducted only if the 84 mg dose group was significant. Sequential testing of the endpoints (in the order 1) Change in MADRS total score, 2) onset of clinical response by Day 2, 3) change in SDS total score, and 4) change in PHQ-9 total score) was performed for both dose groups only if they were significant for the previous endpoint in the hierarchy (84 mg dose group at 2-sided 0.05 level, 56 mg dose group at 2-sided 0.0425 level). If only the 84 mg dose group was significant for an endpoint, testing of the other endpoints down the hierarchy was conducted only for this dose group at the 2-sided 0.0075 level. **Primary efficacy endpoint** Primary efficacy was analysed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate; treatment, region, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects; and a random patient effect. The change from baseline for all post-baseline MADRS assessments (days 2, 8, 15, 22 and 28) were included in the model as the repeated measure. To account for sample size reassessment during the interim analysis, a weighted combination test was used for treatment comparisons, with the test statistic defined as an equally weighted sum of the test statistics determined before (stage 1) and after (stage 2) the interim analysis. The two stages were weighted equally in the combination test. A similar MMRM model was used for a post hoc, unweighted analysis of the primary endpoint combining the 2 ESK-NS dose groups, with the exception that the fixed effect for treatment included pooled ESK-NS + OAD and OAD + PBO-NS groups. Unweighted analyses were also conducted for various subgroups with a similar MMRM model as was used for the primary endpoint. **Secondary efficacy endpoints** <u>Key secondary endpoints</u> • Analysis of the weighted differences in the proportion of patients showing onset of clinical response by day 2 (24 hours) that was maintained for the duration of the double-blind induction phase (day 28) with 1 excursion allowed ((i.e. ≥25% reduction relative to baseline MADRS allowed on days 8, 15, or 22) in the ESK-NS + OAD (both dosing groups 56 mg/84 mg) arm versus OAD + PBO-NS was planned using a Cochran-Mantel-Haenszel chi square test adjusting for country and class of antidepressant (SSRI or SNRI). • The second and third key secondary efficacy endpoints, change from baseline in SDS and PHQ-9 total score at end of double-blind induction phase (day 28),respectively, were analyzed using the MMRM model and weighted combination test described for the primary efficacy analysis but using the respective baseline score (SDS or PHQ-9) as covariate. •
Subgroup analyses	In prespecified exploratory analyses, the point estimate (least squares mean) of the treatment difference (for each treatment comparison) of change from baseline (95% CI) to day 28 for MADRS total score (primary endpoint) were assessed by an

	unweighted MMRA analysis in the double-blind induction phase for each of the following subgroups (full analysis set): • sex (male/female) • age group (<45 years/≥45 years) • baseline MADRS total score (≤Median/>Median) • Number of previous treatment failures in current episode (1 or 2/ 3 or more) • Functional impairment based on baseline SDS (moderate/marked/extreme) • race (black/white/other) • class of antidepressant study medication (SNRI/SSRI)

Table A2a Baseline characteristics and demographics of patients enrolled in TRANSFORM-1 (full analysis set) (19).

	ESK-NS 56 mg + OAD N = 115	ESK-NS 84 mg + OAD N = 114	OAD + PBO-NS N = 113	Total N = 342
Age, years				
Mean (SD)	46.4 (11.18)	45.7 (11.10)	46.8 (11.36)	46.3 (11.19)
Range	22–64	18–64	18–64	18–64
Sex, n (%)				
Male	34 (29.6%)	35 (30.7%)	32 (28.3%)	101 (29.5%)
Female	81 (70.4%)	79 (69.3%)	81 (71.7%)	241 (70.5%)
Race, n (%)				
Asian	2 (1.7%)	1 (0.9%)	2 (1.8%)	5 (1.5%)
Black or African American	7 (6.1%)	7 (6.1%)	5 (4.4%)	19 (5.6%)
White	91 (79.1%)	85 (74.6%)	86 (76.1%)	262 (76.6%)
Other	8 (7.0%)	12 (10.5%)	10 (8.8%)	30 (8.8%)
Multiple	0	0	1 (0.9%)	1 (0.3%)
Not reported	7 (6.1%)	9 (7.9%)	9 (8.0%)	25 (7.3%)
Baseline body mass index (kg/m2)				
Mean (SD)	28.8 (6.70)	28.4 (5.86)	29.2 (6.69)	28.8 (6.42)
Range	18–56	17–50	19–50	17–56
Employment status[a], n (%)				
Any type of employment	60 (52.2%)	67 (58.8%)	67 (59.3%)	194 (56.7%)
Any type of unemployment	41 (35.7%)	41 (36.0%)	36 (31.9%)	118 (34.5%)
Other	14 (12.2%)	6 (5.3%)	10 (8.8%)	30 (8.8%)
Country, n (%)				
Belgium	8 (7.0%)	9 (7.9%)	12 (10.6%)	29 (8.5%)
Brazil	20 (17.4%)	19 (16.7%)	18 (15.9%)	57 (16.7%)
Canada	7 (6.1%)	7 (6.1%)	6 (5.3%)	20 (5.8%)
Estonia	3 (2.6%)	4 (3.5%)	3 (2.7%)	10 (2.9%)
France	11 (9.6%)	10 (8.8%)	10 (8.8%)	31 (9.1%)
Hungary	3 (2.6%)	1 (0.9%)	1 (0.9%)	5 (1.5%)
Mexico	14 (12.2%)	16 (14.0%)	15 (13.3%)	45 (13.2%)

Slovakia	4 (3.5%)	3 (2.6%)	3 (2.7%)	10 (2.9%)
United States	45 (39.1%)	45 (39.5%)	45 (39.8%)	135 (39.5%)
Age when diagnosed with MDD, years				
Mean (SD)	30.3 (12.34)	32.1 (12.86)	31.8 (12.44)	31.4 (12.54)
Range	11–61	9–59	10–63	9–63
Duration of current episode, weeks				
Mean (SD)	202.8 (277.25)	212.7 (327.62)	193.1 (264.10)	202.9 (290.24)
Range	12–1525	12–2288	6–1720	6–2288
No. of previous antidepressant medications[b,c], n (%)				
1 or 2	79 (69.9%)	59 (51.8%)	67 (59.3%)	205 (60.3%)
≥3	34 (30.1)	55 (48.2%)	46 (40.7%)	135 (39.7%)
Class of oral antidepressant[d], n (%)				
SNRI	65 (56.5%)	67 (58.8%)	64 (56.6%)	196 (57.3%)
SSRI	50 (43.5%)	47 (41.2%)	49 (43.4%)	146 (42.7%)
Oral antidepressant, n (%)				
Duloxetine	49 (42.6%)	43 (37.7%)	44 (38.9%)	136 (39.8%)
Escitalopram	26 (22.6%)	23 (20.2%)	24 (21.2%)	73 (21.3%)
Sertraline	24 (20.9%)	24 (21.1%)	25 (22.1%)	73 (21.3%)
Venlafaxine extended release (XR)	16 (13.9%)	24 (21.1%)	20 (17.7%)	60 (17.5%)

Abbreviations: CGI-S, Clinical Global Impression–Severity; MDD, major depressive disorder; PHQ, Patient Health Questionnaire; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Any type of employment includes: any category containing "employed", sheltered work, housewife or dependent husband, and student; any type of unemployment
includes: any category containing "unemployed"; other includes: retired and no information available.

[b]In accordance with the protocol, patients entering the induction phase had nonresponse to at least 2 oral AD medications prior to randomization. The data presented
is the number of AD medications with nonresponse (defined as ≤25% improvement) taken for at least 6 weeks during the current episode as obtained from
Massachusetts General Hospital Antidepressant Treatment Response Questionnaire at the beginning of the screening/prospective observational phase.

[c]Ns for the previous antidepressant medications are 113, 114, 113, and 340 for esketamine 56 mg/antidepressant, esketamine 84 mg/antidepressant, antidepressant/
placebo, and total, respectively.

[d]Assigned by the investigator at randomization.

Table A2.1 Main study characteristics of TRANSFORM-2 (16, 21)

Trial name	TRANSFORM-2
NCT number	NCT02418585
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching adult subjects (18-64 years) with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed ESK-NS (56 mg or 84 mg) plus a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS
Publications – title, author, journal, year	Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study, Popova et al., Am J Psychiatry, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in adult participants (18-64 years) with moderate to severe TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS (56 mg or 84 mg) or PBO-NS. Randomization was balanced by using randomly permuted blocks (blocks size of four) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment. The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. Throughout TRANSFORM-2, and during the double-blind maintenance phase of SUSTAIN-1, the same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of ESk-NS (56 mg/84 mg) or treatment (esketamine versus placebo) they were taking.
Follow-up time	**Double-blind induction phase (4 weeks)** Of the 227 subjects randomly assigned to treatment, 197 (86.8%) subjects completed the 28-day double-blind induction phase, and 30 (13.2%) subjects were withdrawn **Follow-up phase (24 weeks)** 86 subjects entered the follow-up phase, 43 (50.0%) of these subjects completed the follow-up phase and 43 (50.0%) of these subjects were withdrawn from the follow-up phase **Maintenance study rollover (SUSTAIN-1)** 118 subjects continued into the SUSTAIN-1 maintenance of effect study (only responders defined as ≥50% reduction in the MADRS total score from baseline to the end of the 4-week double-blind induction phase were eligible).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the

	country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive • At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participant must have had non-response (greater than or equal to [<=25] percent [%] improvement) to ≥1 but less than or equal to (<=) 5 (if current episode is >2 years, upper limit is applicable to only the last 2 years) oral antidepressant treatments in the current episode of depression, assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented by medical history and pharmacy/prescription records, for the current episode of depression. In addition, the participant is taking a different oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimum therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and antidepressant treatment response in the current depressive episode, must be confirmed using a Site Independent Qualification Assessment **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (i.e., duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive-compulsive disorder, intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria

Intervention	**Double blind Induction phase (4 weeks)** Beginning from the double-blind induction phase, patients (N=227) were randomized 1:1 to receive: • ESk-NS - 56 mg or - 84 mg + OAD (n=116) • Active comparator: OAD + PBO-NS (n=111)
Baseline characteristics	*See table A2.1a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1 prior to randomization) in clinician-administered MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) **Secondary endpoints** The key secondary endpoints assessed: • the proportion of participants with onset of MADRS clinical response by Day 2 (24 hours) that was maintained for the duration of the double-blind phase with 1 excursion (i.e., ≥25% reduction relative to baseline MADRS allowed on days 8, 15 or 22) • Change from baseline in Sheehan Disability Scale (SDS) total score to end of double-blind induction phase • Change from baseline in Patient Health Questionnaire-9 (PHQ-9) total score to end of the double-blind induction phase.
Method of analysis	**Sample Size, power calculation** The sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, a SD of 12, based on the results of a phase 2 study of ESK-NS for TRD (SYNAPSE) and clinical judgment, a 2-sided significance level of 0.05, and a drop-out rate of 25%. 98 patients were required to be randomized to each treatment group to achieve 90% power using a fixed design assuming no interim analysis. **Efficacy analyses** Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase) using a truncated fixed sequence parallel gatekeeping procedure to adjust for multiplicity and to strongly control type I error across the primary (change in MADRS total score) and the 3 key secondary efficacy endpoints (onset of clinical response by Day 2, change in SDS total score, and change in PHQ-9 total score). Statistical tests were conducted at a two-sided significance level 0.05. **Primary efficacy endpoint** Primary efficacy endpoint, change in MADRS score from baseline (day 1) to endpoint (day 28) of the double-blind induction phase was analyzed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate and treatment, country, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects; and a random patient effect. A delta adjustment

	tipping point sensitivity analysis was conducted to evaluate the robustness of the MMRM analysis to increasing deviations from the missing-at-random assumption **Secondary efficacy endpoints** The three key secondary endpoints were analyzed sequentially and considered significant at the two-sided 0.05 level only if the endpoint individually and previous endpoints in the hierarchy, including the primary endpoint, were significant at the two-sided 0.05 level. • The first key secondary efficacy endpoint compared the proportion of participants with onset of clinical response in MADRS score by day 2 with 1 excursion (i.e. ≥25% reduction relative to baseline MADRS allowed on days 8, 15, or 22) maintained to the end of the double-blind induction phase using a Cochran-Mantel-Haenszel chi-square test adjusting for country and antidepressant class. • The second and third key secondary efficacy endpoints- change from baseline to week 4 in SDS and PHQ-9 scores, respectively – were analyzed using the MMRM model described for the primary efficacy analysis but using the respective baseline score for the instrument as a covariate. •
Subgroup analyses	Prespecified exploratory subgroup analyses included age, sex, baseline severity, antidepressant class, number of previous treatment failures, functional impairment, and region

Table A2.1a Baseline characteristics and demographics of patients enrolled in TRANSFORM-2 (full analysis set) (16)

Characteristic	ESK-NS + OAD (N=114)		OAD + PBO-NS (N=109)	
	Mean	SD	Mean	SD
Age (years)	44.9	12.58	46.4	11.14
Age at diagnosis of major depression (years)	32.1	12.53	35.3	13.04
Duration of current episode (weeks)	111.4	124.28	118.0	187.37
Montgomery-Åsberg Depression Rating Scale score	37.0	5.69	37.3	5.66
Body mass index (calculated as kg/m2)	27.5	5.84	28.6	6.24
	N	%	N	%
Sex				
Male	39	34.2	46	42.2
Female	75	65.8	63	57.8
Race				
Asian	1	0.9	1	0.9
Black or African American	6	5.3	5	4.6

White	106	93.0	102	93.6
Multiple	1	0.9	1	0.9
Employment status[a]				
Any type of employment	68	59.6	63	57.8
Any type of unemployment	34	29.8	35	32.1
Other	12	10.5	11	10.1
Country				
Czech Republic	30	26.3	28	25.7
Germany	10	8.8	10	9.2
Poland	20	17.5	18	16.5
Spain	9	7.9	9	8.3
United States	45	39.5	44	40.4
Number of previous antidepressant medications[b]				
1 or 2	78	68.4	72	66.1
≥3	36	31.6	37	39.9
Class of antidepressant				
Serotonin-norepinephrine reuptake inhibitor	77	67.5	75	68.8
Selective serotonin reuptake inhibitor	37	32.5	34	31.2
Antidepressant				
Duloxetine	60	52.6	61	56.0
Escitalopram	21	18.4	17	15.6
Sertraline	16	14.0	16	14.7
Venlafaxine extended-release	17	14.9	15	13.8

[a] Any type of employment includes any category containing “employed,” sheltered work, housewife or dependent husband, and student; any type of unemployment
includes any category containing “unemployed”; “other” includes retired and no information available.
[b] Number of previous antidepressant medications indicates antidepressants taken for at least 6 weeks with nonresponse (defined as #25% improvement) during
the current episode in addition to one prospective antidepressant.

Table A2.2 Main study characteristics of TRANSFORM-3 (18, 22)

Trial name	TRANSFORM-3
NCT number	NCT02422186
Objective	The purpose of this study is to evaluate the efficacy, safety and tolerability of switching elderly subjects (≥65 years) with TRD from a prior antidepressant treatment (to which they have not responded) to flexibly dosed ESk-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD or to a newly initiated OAD (active comparator) + PBO-NS.
Publications – title, author, journal, year	Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients with Treatment-Resistant Depression – TRANSFORM-3, Am J of Geriatric Psychiatry, 2019
Study type and design	This is a phase 3, randomized, double-blind, active-controlled, multicenter study in elderly participants (≥65 years) with TRD (nonresponse to ≥1 to ≤8 antidepressants in the current depression episode) to assess the efficacy, safety, and tolerability of flexibly dosed ESK-NS (28 mg, 56 mg or 84 mg) + a newly initiated OAD (escitalopram, sertraline, duloxetine or venlafaxine XR) compared with a newly initiated OAD (active comparator: escitalopram, sertraline, duloxetine or venlafaxine XR) + PBO-NS. Eligible subjects were randomly assigned at a 1:1 ratio by computer-generated randomization schedule (IWRS randomization codes) to either ESK-NS (56 mg or 84 mg) or PBO-NS. Randomization was balanced by using randomly permuted blocks (block size of four) and was stratified by country and by class of oral antidepressant (SSRI or SNRI). Patients, investigators, site personnel, those assessing outcomes, and those analyzing the data were blind to treatment assignment The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug.
Follow-up time	**Double-blind induction phase (4 weeks)** Of the 138 subjects randomly assigned to treatment, 122 (88.4%) subjects completed the 28-day double-blind induction phase, and 16 (11.6%) subjects were withdrawn. A total of 77.8% patients in the ESK-NS + OAD, and 81.5% in the OAD + PBO-NS group received treatment on all eight dosing days. **Follow-up phase (24 weeks)** 15 (10.9%) subjects entered the follow-up phase, 11 (73.3%) of these subjects completed the follow-up phase and 4 (33.3%) of these subjects were withdrawn from the follow-up phase **Maintenance study rollover (SUSTAIN-2, not part of this application)** 111 (80.4%) subjects continued into the SUSTAIN-2 (NCT02497287) long-term safety and efficacy study and 2 (1.4%) subjects continued into SUSTAIN-3 (NCT02782104, not part of this application) long-term safety extension study after completing the 28-day double-blind induction phase
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • At the time of signing the informed consent form (ICF), participant must be a man or woman 65 years of age or older • At the start of the Screening/prospective observational Phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) [if single-episode MDD, the duration must be greater than or equal to (>=) 2

	years] or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the Screening/Prospective observational Phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 31 • At the start of the Screening/Prospective observational Phase, participants must have had nonresponse (less than or equal to 25% improvement) to >=1 but less than or equal to (<=) 8 oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and documented records by medical and pharmacy/prescription records, or a letter from the treating physician, for the current episode of depression • Participant must be taking one of the oral antidepressant treatments with nonresponse that is documented on the MGH-ATRQ at the start of the screening/prospective observational phase • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score greater than or equal to 24 required) and treatment response to antidepressant treatments used in the current depressive episode (retrospectively assessed) must be confirmed for participation in a clinical study based on a Site-Independent Qualification Assessment • Participant must be medically stable on the basis of clinical laboratory tests performed in the screening/prospective observational phase **Exclusion Criteria:** • The participant's depressive symptoms have previously demonstrated nonresponse to: Esketamine or ketamine in the current major depressive episode per clinical judgment, or all of the 4 oral antidepressant treatment options available for the double-blind induction Phase (Duloxetine, Escitalopram, Sertraline, and Venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral ECT • Participants who has received vagal nerve stimulation (VNS) or who has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current episode only), intellectual disability (intellectual disability [DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319]), borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the Investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the Screening/prospective observational Phase, per the Investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) and also includes history of suicidal behavior within the past year prior to start of the screening/prospective observational phase • Participant has a history (lifetime) of ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3, 4-methylenedioxy-methamphetamine (MDMA) hallucinogen-related use disorder • Participant has a Mini Mental State Examination (MMSE) < 25 or <22 for those participants with less than an equivalent of high school education

	• Participant has neurodegenerative disorder (e.g., Alzheimer's Disease, Vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI) • Participant has a history of uncontrolled hypertension; current or past history of significant pulmonary insufficiency/condition; clinically significant ECG abnormalities; current or past history of seizures; clinically significant cardiovascular disorders including cerebral and cardiac vascular disease
Intervention	**Double blind Induction phase (4 weeks)** ESK-NS 28 mg, 56 mg or 84 mg + OAD (n=72) Active comparator: OAD + PBO-NS (n=66)
Baseline characteristics	*See table A2.2a*
Primary and secondary endpoints	**Primary endpoints** The primary efficacy endpoint was improvement in depressive symptoms as assessed by the change from baseline (day 1) in MADRS total score (independent, remote rater) to the end of the 4-week double-blind induction phase (Day 28) **Secondary endpoints** Secondary endpoints included: • Rates of response (≥50% reduction from baseline in the MADRS total score) at double-blind induction phase (day 28) • Rates of remission (MADRS ≤12 at endpoint) at double-blind induction phase (day 28) • Change from baseline to endpoint of double-blind induction phase in: • CGI-S total score • PHQ-9 total score • SDS total score
Method of analysis	**Sample Size, power calculation** The maximum sample size planned was calculated assuming a treatment difference for the double-blind induction phase of 6.5 points in MADRS total score between ESK-NS + OAD and the OAD + PBO-NS arms, a SD of 12, based on the results of a phase 2 study of esketamine nasal spray for treatment-resistant depression (SYNAPSE, NCT01998958) and clinical judgment, a 2-sided significance level of 0.05, and a drop-out rate of 25%. 74 patients were required to be randomized to each treatment group to achieve 80% power using a fixed design assuming no interim analysis (IA). **Efficacy analyses** Efficacy analyses were performed on the full analysis set (all randomized subjects who received at least 1 dose of intranasal study mediation and 1 dose of oral antidepressant medication during the double-blind induction phase). Statistical tests were conducted at a two-sided significance level 0.05 unless otherwise specified. **Primary efficacy endpoint** Primary efficacy endpoint changes in MADRS score from baseline (day 1) to endpoint (day 28) of the double-blind induction phase was analyzed using a mixed-effects repeated measures model (MMRM) with baseline MADRS total score as a covariate and treatment, region, oral antidepressant class (SNRI or SSRI), day, and day-by-treatment interaction as fixed effects. Least square means (i.e., adjusted for terms included in the MMRM model) were provided for each timepoint. To adjust for the interim analysis (IA), the primary endpoint was analyzed using a weighted combination test that defined test statistics from the MMRM analyses as a weighted sum of stage 1

	(pre-IA) and stage 2 (post-IA) test statistics. Stages were weighted equally regardless of the sample size in each stage. The median-unbiased estimate and flexible CI were used for estimation of the treatment difference from antidepressant/placebo at Day 28. **Secondary efficacy endpoints** Additional measures of efficacy including: • The proportion of responders (≥50% reduction from baseline in MADRS total score) and remitters (MADRS ≤12) at end of double-blind induction phase • The average number of patients needed to produce one more responder/remitter in the ESK-NS + OAD group than in the OAD + PBO-NS group was calculated for response and remission. • The odds ratio for an improved CGI-S was estimated by mapping the ordinal scale to a continuous scale using item response modeling via the logit model and analyzed using an ANCOVA model. • Descriptive statistics of actual values and changes from baseline to end of double-blind induction phase in PHQ-9 and SDS total score. • The number needed to treat (NNT) was estimated for both response and remission at day 28 on the MADRS total score
Subgroup analyses	Preplanned assessment of age (65-74 or ≥75 years) and a post-hoc assessment of age at MDD onset (<55 or ≥55 years) by the change from baseline (day 1) in MADRS total score to the end of the double-blind induction phase using MMRM models with baseline MADRS total score as a covariate, and treatment, region, class of antidepressant (SSRI or SNRI), age, day, treatment-by-day, treatment-by-age and treatment by-day-by-age interaction as fixed effects..

Table A2.2a Baseline characteristics and demographics of patients enrolled in TRANSFORM-3 (full analysis set) (18)

	ESK-NS + OAD (N = 72)	OAD + PBO-NS (N = 65)	Total (N = 137)
Age (years), mean (SD)	70.6 (4.79)	69.4 (4.15)	70.0 (4.52)
Male	27 (37.5)	25 (38.5)	52 (38.0)
Female	45 (62.5)	40 (61.5)	85 (62.0)
Age category (years), n (%)			
65−74	59 (81.9)	57 (87.7)	116 (84.7)
≥75	13 (18.1)	8 (12.3)	21 (15.3)
Race, n (%)			
White	66 (91.7)	64 (98.5)	130 (94.9)
Multiple	4 (5.6)	0	4 (2.9)
Not reported	1 (1.4)	1 (1.5)	2 (1.5)
Unknown	1 (1.4)	0	1 (0.7)
Region, n (%)			
European Union	35 (48.6)	24 (36.9)	59 (43.1)
United States	34 (47.2)	36 (55.4)	70 (51.1)
Other	3 (4.2)	5 (7.7)	8 (5.8)
Class of oral AD, n (%)			
SNRI	31 (43.1)	30 (46.2)	61 (44.5)
SSRI	41 (56.9)	35 (53.8)	76 (55.5)
Oral AD			
Duloxetine	25 (34.7)	23 (35.4)	48 (35.0)
Escitalopram	25 (34.7)	25 (38.5)	50 (36.5)
Sertraline	15 (20.8)	10 (15.4)	25 (18.2)
Venlafaxine XR	7 (9.7)	7 (10.8)	14 (10.2)

Age when diagnosed with MDD (years), mean (SD)	42.6 (16.18)	43.7 (16.28)	43.1 (16.18)
Baseline MADRS total score, mean (SD)	35.5 (5.91)	34.8 (6.44)	35.2 (6.16)[a]
Screening IDS-C30 total score, mean (SD)	44.2 (6.50)	43.1 (6.71)	43.7 (6.60)
Duration of current episode (weeks), mean (SD)	163.1 (277.04)	274.1 (395.47)	215.8 (341.71)
Baseline CGI-S, mean (SD)	5.1 (0.76)	4.8 (0.80)	5.0 (0.79)
Number of previous AD trial in addition to 1 AD trial assessed prospectively,[b] n (%)			
1	15(20.8)	6 (9.2)	21 (15.3)
2	31 (43.1)	32 (49.2)	63 (46.0)
3	13 (18.1)	17 (26.2)	30 (21.9)
4	12 (16.7)	4 (6.2)	16 (11.7)
≥5	1 (1.4)	6 (9.2)	7 (5.1)

AD: antidepressant; CGI-S: Clinical Global Impression-Severity; Esk: esketamine; IDS-C30: Inventory of Depressive Symptoms-Clinician rated-30-
item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MGH-ATRQ: Massachusetts General Hospital Antidepressant
Treatment Response Questionnaire; SD: standard deviation; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin
reuptake inhibitor; XR: extended release.

[a] Range: 19–51. In some cases, the baseline MADRS score was obtained after patients were qualified to enter the trial so the baseline MADRS
could be ≤24.

[b] Number of antidepressant medications with nonresponse (defined as <25% improvement) taken for at least 6 weeks during the current episode
as obtained from MGH-ATRQ.

Table A2.3 Main study characteristics of SUSTAIN-1 (17, 23)

Trial name	SUSTAIN-1

NCT number	NCT02493868
Objective	The purpose of this study is to assess the efficacy of flexibly doses ESK-NS + OAD (56 mg/84 mg) compared with OAD (active comparator) + PBO-NS in delaying relapse of depressive symptoms in adult patients (18-64 years) with treatment-resistant depression (TRD) who are in stable remission and response after an induction (4 weeks) and optimization (12 weeks) course of ESK-NS + OAD. Additionally, to investigate the safety and tolerability of ESK-NS + OAD compared with OAD + PBO-NS.
Publications – title, author, journal, year	Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients with Treatment-Resistant Depression, Daly et al., JAMA Psychiatry, 2019
Study type and design	This is a phase 3, double-blind, active-controlled, multicenter, relapse prevention study using a randomized withdrawal design* in adults (18-64 years) with TRD (nonresponse to ≥1 to≤5 antidepressants in the current depression episode) who have achieved stable remission or stable response after an induction and optimization course of treatment with ESK-NS + OAD. The study compared the maintenance of efficacy of continued flexibly-doses ESK-NS + OAD treatment with that of OAD + PBO-NS. The study continued until requisite number of relapses occurred, specified by a preplanned interim analysis (31 relapses to assess early efficacy) Investigators and site personnel were not provided with the IWRS randomization codes a remained blinded to treatment assignments until all patients had completed the study. The ESK-NS and PBO-NS devices were indistinguishable. A bittering agent (denatonium benzoate) was added to the placebo solution to simulate the taste of the nasal spray solution containing active drug. * Subjects were randomized in a 1:1 ratio in the maintenance phase to either continue ESK-NS (same dose) or to discontinue ESK-NS; all subjects continued the same OAD, at the same dose. Randomization was achieved centrally via an IWRS, balanced using randomly permuted blocks (block size of four), stratified by country. The same number of nasal spray devices (three) were given to patients to self-administer regardless of what dose of ESK-NS (56 mg/84 mg) or treatment (esketamine or placebo) they were taking. Transfer entry patients who achieved stable remission or stable response at the end of the optimization phase after treatment with an OAD + PBO-NS continued to receive the same treatment.
Follow-up time	**Time frame: baseline and endpoint (up to 92 weeks):** **Induction phase (4 weeks):** Of the 437 safety set subjects (direct-entry subjects only, 273 (62.5%) subjects completed the 28-day induction phase and 164 (37.5%) subjects withdrew **Optimization phase (12 weeks):** Of the 455 esketamine-treated subjects entering the optimization phase (including 182 esketamine-treated transferred-entry subjects), 297 (65.3%) completed the 12-week optimization phase and 158 (34.7%) subjects withdrew. **Maintenance phase (variable length:** <u>Remitters</u>

	Of the 176 subjects in the Full (stable remitters) analysis set, 159 (90.3%) subjects completed the maintenance phase. Median exposure to ESK-NS during the maintenance phase was 17.7 weeks in stable remitters and 19.4 weeks in stable responders. <u>Responders</u> Of the 121 subjects in the Full (stable responders) analysis set, 113 (93.4%) subjects completed the maintenance phase. Median exposure to PBO-NS during the maintenance phase was 10.2 weeks among stable remitters and 10.1 weeks among stable responders
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** <u>For Direct-Entry Participants</u> • At the time of signing the informed consent form (ICF), participant must be a man or woman 18 (or older if the minimum legal age of consent in the country in which the study is taking place is greater than [>]18) to 64 years of age, inclusive - At the start of the screening/prospective observational phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At the start of the screening/prospective observational phase, participant must have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of greater than or equal to (>=) 34 • At the start of the screening/prospective observational phase, participants must have had nonresponse (less than or equal to 25 percent [%] improvement) to greater than or equal to (>=1) but less than or equal to (<=) 5 oral antidepressant treatments taken at adequate dosage and for adequate duration, as assessed using the Massachusetts General Hospital (MGH-ATRQ) • MGH-ATRQ and documented by medical history and pharmacy/prescription records, for the current episode of depression. In addition, the participant is taking different ongoing oral antidepressant treatment (on the MGH-ATRQ) for at least the previous 2 weeks at or above the minimal therapeutic dose • The participant's current major depressive episode, depression symptom severity (Week 1 MADRS total score >=28 required), and treatment response to antidepressant treatments used in the current depressive episode (retrospectively assessed) must be deemed valid for participation in a clinical study based on a Site-Independent Qualification Assessment for Transferred-Entry Participants • The participant must have completed the double-blind induction phase in TRANSFORM-1 or TRANSFORM-2 and must have demonstrated response at the end of that phase (>=50% reduction in the MADRS total score from baseline [Day 1 pre-randomization] at the end of the 4-week double-blind induction phase) **Exclusion Criteria:** • Participants who have previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine in the current major depressive episode, to all 4 of the oral antidepressant treatment options available for

	the double-blind induction phase (i.e., duloxetine, escitalopram, sertraline, and venlafaxine extended release [XR]) in the current major depressive episode (based on MGH-ATRQ), or an adequate course of treatment with electroconvulsive therapy (ECT) in the current major depressive episode, defined as at least 7 treatments with unilateral/bilateral ECT • Participant has received vagal nerve stimulation (VNS) or has received deep brain stimulation (DBS) in the current episode of depression • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria
Intervention	<u>Intranasal esketamine 56 mg or 84 mg plus oral antidepressant</u> ***Open label induction phase (direct-entry patients only; n=437)*:** ***Optimization phase (direct-entry and transferred-entry patients (TRANSFORM1/2); n=455):*** ***Maintenance phase (n=297)*:** Patients in stable remission (n=176) were randomized 1:1 to either: • Continued with ESK-NS (same dose) and the same OAD (n=90), or • Continued with the same OAD, but switched to PBO-NS(n=86) Patients with stable response (but who were not in stable remission; n=121) were randomized 1:1 to either: • Continued with ESK-NS (same dose) and the same OAD (n=62), or • Continued with the same OAD but switched to PBO-NS (n=59,)
Baseline characteristics	*See table A2.3a*
Primary and secondary endpoints	**Primary efficacy endpoint** Primary efficacy endpoint was the time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable remission at the end of optimization phase after treatment with ESK-NS + OAD (based on MADRS) **Secondary and other efficacy endpoints** Key secondary endpoint: • time from randomization to the first relapse during the maintenance phase (up to 92 weeks) in esketamine-treated subjects who achieved stable response (not in remission) at the end of the optimization phase after treatment with ESK-NS + OAD (based on MADRS)
Method of analysis	SUSTAIN-1 was implemented as a random withdrawal design to perform analyses on time to relapse (i.e. survival analyses). As such, the follow-up duration was different

	between patients, depending on their inclusion date and time remaining until study termination. The study was not set up to analyse patients' outcomes at fixed timepoints. For this reason, response and remission rates over time were not measured at a fixed date but at the endpoint, which corresponds to the last record available for the patients. This can be viewed as analysis of covariance (ANCOVA) based on last observation carried forward (LOCF) at the longest observed follow-up per patient. **Sample Size, power calculation** On the basis of assumptions, 211 patients who achieved stable remission needed to be randomized (1:1 ratio) to obtain 84 relapses, providing 90% power to detect a HR of 0.49 at a 2-sided alpha of 0.05 for a fixed-sample design to detect superiority of ESK-NS + OAD over OAD + PBO-NS in delaying time to relapse of depressive symptoms. A 2-stage group-sequential design was implemented for the analysis set of patients who achieved stable remission, and an independent data-monitoring committee performed a pre-specified interim analysis at 31 relapses to assess early efficacy. **Efficacy endpoints** The primary efficacy analysis was based on the full (stable remitters) analysis set and the relapse (based on MADRS total score) collected during the maintenance phase. The cumulative distribution function of time to relapse during the maintenance phase among patients who achieved stable remission (primary endpoint) and those who achieved stable response without remission (secondary endpoint) was estimated by the Kaplan-Meier method. Relapse was defined as a MADRS total score of 22 or higher for 2 consecutive assessments separated by 5 to 15 days or hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or another clinically relevant event suggestive of relapse (assessed by a relapse adjudication committee) The between-group difference in time to relapse was analyzed using a 2-sided log-rank test (weighted combination [interim and final analyses] for patients who achieved stable remission because of conducting an interim analysis). The estimated HRs and 95% CIs were based on weighted estimates for patients who achieved stable remission and, on a Cox proportional hazards regression model with treatment as a factor for patients who achieved stable response. A similar post hoc analysis was performed combining the analysis set of patients who achieved stable remission and the analysis set of patients who achieved stable response
Subgroup analyses	n/a

Table A2.3a Baseline characteristics of SUSTAIN-1 (17)

Characteristic[a]	Stable Remission at Baseline		Stable Response at Baseline	
	ESK-NS + OAD (n = 90)	OAD + PBO-NS (n = 86)	ESK-NS + OAD (n = 62)	OAD + PBO-NS (n = 59)
Age, mean (SD) [range], y	45.4 (12.12) [19-64]	46.2 (11.16) [19-64]	47.2 (11.00) [23-63]	46.7 (9.76) [24-64]
Sex				
Male	32 (35.6)	27 (31.4)	24 (38.7)	17 (28.8)
Female	58 (64.4)	59 (68.6)	38 (61.3)	42 (71.2)
Race				
American Indian or Alaskan Native	0	1 (1.2)	0	0
Asian	0	0	0	1 (1.7)
Black	4 (4.4)	6 (7.0)	2 (3.2)	1 (1.7)
White	80 (88.9)	76 (88.4)	57 (91.9)	55 (93.2)
Other	2 (2.2)	1 (1.2)	3 (4.8)	1 (1.7)
Multiple	1 (1.1)	0	0	1 (1.7)
Not reported	3 (3.3)	2 (2.3)	0	0
Region				
Europe	52 (57.8)	50 (58.1)	34 (54.8)	35 (59.3)
North America	22 (24.4)	20 (23.3)	18 (29.0)	16 (27.1)
Brazil and Mexico	16 (17.8)	16 (18.6)	10 (16.1)	8 (13.6)
Age diagnosed with MDD, mean (SD) [range], y	32.5 (11.42) [5-55]	33.4 (11.41) [10-60]	36.2 (13.25) [15-61]	34.0 (10.54) [14-60]
Duration of current episode, mean (SD) [range], wk	112.2 (171.30) [12-1040]	110.5 (147.41) [9-884]	121.6 (193.85) [13-1080]	141.8 (254.43) [9-1248]
No. of previous antidepressants before screening				
≤2	71 (78.9)	62 (73.8)	41 (66.1)	34 (57.6)
>2	19 (21.1)	22 (26.2)	21 (33.9)	25 (42.4)
History of suicidal ideation in previous 6mo	18 (20.0)	14 (16.3)	20 (32.3)	14 (23.7)
Class of oral antidepressant				
SNRI	62 (68.9)	58 (67.4)	35 (56.5)	36 (61.0)
SSRI	28 (31.1)	28 (32.6)	27 (43.5)	23 (39.0)
Baseline MADRS total score, mean (SD)				
All patients	37.4 (5.20)	37.6 (4.66)	40.1 (5.56)	38.9 (4.92)
Direct-entry patients[b]	37.8 (5.28)	37.8 (4.26)	40.5 (4.88)	38.5 (4.65)
Transfer-entry patients[c]	36.8 (5.10)	37.3 (5.38)	39.6 (6.22)	39.9 (5.49)
Baseline PHQ-9 score, mean (SD)	19.2 (4.16)	19.8 (3.43)	20.5 (4.12)	20.4 (4.15)
Dose of esketamine before randomization[d]				
56 mg	40 (44.4)	33 (38.4)	20 (32.3)	19 (32.2)
Direct-entry patients	14 (15.6)	9 (10.5)	7 (11.3)	6 (10.2)

Transfer-entry TRANSFORM-1 patients[e]	5 (5.6)	4 (4.7)	5 (8.1)	3 (5.1)
Transfer-entry TRANFORM-2 patients[f]	21 (23.3)	20 (23.3)	8 (12.9)	10 (16.9)
84 mg	50 (55.6)	53 (61.6)	42 (67.7)	40 (67.8)
Direct-entry patients	12 (13.3)	11 (12.8)	8 (12.9)	2 (3.4)
Transfer-entry TRANFORM-1 patients[e]	5 (5.6)	6 (7.0)	11 (17.7)	7 (11.9)
Transfer-entry TRANFORM-2 patients[f]	33 (36.7)	36 (41.9)	23 (37.1)	31 (52.5)
Dosing frequency at baseline				
Weekly	37 (41.1)	41 (47.7)	51 (83.6)	43 (72.9)
Every other week	53 (58.9)	45 (52.3)	10 (16.4)	16 (27.1)
Missing	0	0	1	0

Abbreviations: MADRS, Montgomery-Asberg Depression Rating scale; MDD, major depressive disorder; PHQ-9, Patient Health Questionnaire 9; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Patients who achieved stable remission: 54 for esketamine nasal spray and oral antidepressant and 56 for oral antidepressant and placebo nasal spray; patients who achieved stable response: 31 for esketamine nasal spray and oral antidepressant and 41 for oral antidepressant and placebo nasal spray.

[c] Patients who achieved stable remission: 36 for esketamine nasal spray and oral antidepressant and 30 for oral antidepressant and placebo nasal spray; patients who achieved stable response: 31 for esketamine nasal spray and oral antidepressant and 18 for oral antidepressant and placebo nasal spray.

[d] During the optimization phase and before randomization.

[e] transferred from Janssen-sponsored fixed-dose esketamine study TRANFORM-1.

[f] transferred from Janssen-sponsored flexible-dose esketamine study TRANFORM-2.

Table A2.4 Main study characteristics of SUSTAIN-2 (33, 34)

Trial name	SUSTAIN-2
NCT number	NCT02497287
Objective	The purpose of this open-label, multicenter study is to assess the long term safety and efficacy of intranasal esketamine plus an oral antidepressant in participants with treatment-resistant depression (TRD).
Publications – title, author, journal, year	Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). The Journal of clinical psychiatry. 2020;81
Study type and design	This is an open-label (the researchers and participants know the treatment the participant is receiving), multicenter (more than 1 study site), long-term safety and efficacy study of intranasal esketamine plus an oral antidepressant in participants with treatment-resistant depression (TRD). Participants will enter the study either directly (direct-entry participants) or after completing the Double-Blind Induction Phase of TRANSFORM-3 (transferred-entry participants). The study consists of 4 phases: Screening Phase (4 weeks), Open-Label Induction Phase (4 weeks), Open-Label Optimization/Maintenance phase (48 weeks), and Follow up Phase (4 weeks). Transferred entry non-responders in the TRANSFORM-3 may enter study at the Open-Label Induction Phase and responders in the TRANSFORM-3 may enter Optimization/Maintenance phase
Follow-up time	Follow up Phase (4 weeks). Time Frame: Week 52 Up to End of Follow up Phase Week 56)
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** For Direct-Entry Participants • At the time of signing the informed consent form (ICF), participant must be a man or woman ≥18 (or older if the minimum legal age of consent in the country in which the study is taking place is greater than [>]18) • At the start of the screening phase, participant must meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for single-episode major depressive disorder (MDD) (if single-episode MDD, the duration must be greater than or equal to [>=] 2 years) or recurrent MDD, without psychotic features, based upon clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) • At screening, participant must have a MADRS total score of >=22 • At the start of the screening phase, participants must have had nonresponse to >=2 oral antidepressant treatments in the current episode of depression, as assessed using the the MGHATRQ and confirmed by documented records (example medical/pharmacy/prescription records or a letter from treating a physician, etc,) B). For Transferred-entry Participants • All participants who completed the double-blind induction phase of TRANFORM-3 study, regardless of their response status, will be eligible to participate in this study, if they meet the study specific eligibility criteria **Exclusion Criteria:** For Direct-Entry Participants

	• Participant's depressive symptoms have previously not responded to: Esketamine or ketamine in the current major depressive episode per clinical judgment or All of the 4 oral antidepressant treatment options available in the respective country for the open-label induction phase (that is, duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current major depressive episode (based on Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire [MGH-ATRQ]) • Participant has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar or related disorders (confirmed by the MINI), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder • Participant has homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 6 months prior to the start of the screening phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) • Participants with history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria • Participants who has a Mini Mental State Examination (MMSE) <25; Has neurodegenerative disorder (example, Alzheimer's disease, vascular dementia, Parkinson's disease), or evidence of mild cognitive impairment (MCI) B). Transferred-Entry Participants • Participant has taken any prohibited therapies that would not permit dosing on Day 1
Intervention	• Drug: Esketamine (Intranasal Spray) Open-Label Induction Phase: Participants will self-administer esketamine intranasally twice per week for 4 weeks as a flexible dose regimen (56 mg or 84 mg for those < 65 years; 28 mg, 56 mg or 84 mg for those >= 65 years). Participants >= 65 years old will start at a dose of 28 mg on Day 1. Optimization/Maintenance Phase: Participants will self-administer esketamine intranasally (56 mg or 84 mg for those < 65 years; 28 mg, 56 mg or 84 mg for those >= 65 years) once weekly then individualized to either once weekly or once every other week based on the severity of depressive symptoms. Transferred-entry responder participants from TRANSFORM-3 >= 65 years old will start at a dose of 28 mg in Week 5. • Drug: Duloxetine (Oral Antidepressant) Duloxetine could be selected as the oral antidepressant medication by the investigator based on review of Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) and relevant prior antidepressant medication information. The minimum therapeutic dose is 60 milligram per day (mg/day). • Drug: Escitalopram (Oral Antidepressant) Escitalopram could be selected as the oral antidepressant medication by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information. The

	minimum therapeutic dose is 10 mg/day. Participants >= 65 years of age will be titrated up to 20 mg/day, but can lower the dose to 10 mg/day for tolerability. • Drug: Sertraline (Oral Antidepressant) Sertraline could be selected as the oral antidepressant medication by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information. Sertraline will be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 50 mg/day. • Drug: Venlafaxine Extended Release (XR) (Oral Antidepressant) Venlafaxine Extended Release could be selected as the oral antidepressant medication by the investigator based on review of MGH-ATRQ and relevant prior antidepressant medication information. Venlafaxine Extended Release will be titrated for participants < 65 years of age up to a dose of 225 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 150 mg/day. For participants >= 65, it can be titrated up to a dose of 150 mg/day, but if not tolerated the dose can be reduced to the minimum therapeutic dose of 75 mg/day.
Baseline characteristics	*See table A2.4a*
Primary and secondary endpoints	Primary endpoints • Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) [Time Frame: Up to End of Follow up Phase (Week 56)] • Percentage of Participants With Cystitis, Urinary Tract Infections, Renal and Urinary Tract Symptoms, Renal and Urinary Disorders [Time Frame: Up to End of Follow up Phase (Week 56)] • Change From Baseline in Cognitive Test Battery: Detection Test (DET) Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of Optimization/Maintenance [OP/MA] Phase)] • Change From Baseline in Cognitive Test Battery: Identification Test (IDN) Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline in Cognitive Test Battery: One Card Learning Test (OCL) Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline in Cognitive Test Battery: One Back Test (ONB) Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline in Cognitive Test Battery: Groton Maze Learning Test (GMLT) Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of • Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Total Recall [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)]

	• Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Delayed Recall [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Number of Words Recalled [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score: Recognition Discrimination Index [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] Secondary endpoints • Change From Baseline to Endpoint in Montgomery Asberg Depression Rating Scale (MADRS) Total Score During Induction (IND) Phase [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in MADRS Total Score During Optimization/Maintenance (OP/MA) Phase [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA Phase)] • Change From Baseline to Endpoint in Patient Health Questionnaire - 9 (PHQ-9) Total Score During IND Phase [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in PHQ-9 Total Score During OP/MA Phase [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline to Endpoint in Clinical Global Impression of Severity (CGI-S) Scale Score During IND Phase [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in CGI-S Scale Score During OP/MA Phase [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline to Endpoint in Generalized Anxiety Disorder (GAD-7) Total Score During IND Phase [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in GAD-7 Total Score During OP/MA Phase [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline to Endpoint in European Quality of Life (EuroQol) 5-Dimension, 5-Level (EQ 5D-5L) During IND Phase: Sum Score [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in EQ-5D-5L Score During IND Phase: EQ-VAS [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)]

	• Change From Baseline to Endpoint in EQ-5D-5L Scale Score During IND Phase: Health Status Index [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Change From Baseline to Endpoint in European Quality of Life (EuroQol) 5-Dimension, 5-Level (EQ 5D-5L) During OP/MA Phase: Sum Score [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline to Endpoint in EQ-5D-5L Score During OP/MA Phase: EQ-VAS [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline to Endpoint in EQ-5D-5L Scale Score During OP/MA Phase: Health Status Index [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Change From Baseline in Sheehan Disability Scale (SDS) Total Score During IND Phase [Time Frame: Baseline (IND) up to the Endpoint (last post-baseline assessment value during 4 weeks of IND Phase)] • Change From Baseline in Sheehan Disability Scale Total Score During OP/MA Phase [Time Frame: Baseline (OP/MA) up to the Endpoint (last post-baseline assessment value during 52 weeks of OP/MA phase)] • Percentage of Participants With Response as Assessed by MADRS Total Score During IND Phase [Time Frame: Days 8, 15, 22 and Endpoint (last post-baseline assessment during 4 weeks of IND phase)] • Percentage of Participants With Response as Assessed by PHQ-9 Total Score During IND Phase [Time Frame: Day 15 and Endpoint (last post-baseline assessment value during 4 Week IND phase)] • Percentage of Participants With Remission as Assessed by MADRS Total Score During IND Phase [Time Frame: Days 8, 15, 22 and Endpoint (last post-baseline assessment value during 4 weeks of IND Phase)]. • Percentage of Participants With Remission as Assessed by PHQ-9 Total Score During IND Phase [Time Frame: Day 15 and Endpoint (last post-baseline assessment value during 4 weeks of IND phase)] • Percentage of Participants With an Increase Score From Predose at Any Time in Clinician-Administered Dissociative States Scale (CADSS) Total Score During IND Phase [Time Frame: Predose, up to 1.5 hours postdose (up to end of IND phase [Week 4])] • Percentage of Participants With an Increase Score From Predose at Any Time in CADSS Total Score During OP/MA Phase [Time Frame: Predose, up to 1.5 hours postdose (up to end of OP/MA phase [Week 52])] • Percentage of Participants With Treatment-Emergent Acute Hypertension (Systolic and Diastolic) During IND and OP/MA Phases [Time Frame: Up to End of OP/MA phase (Week 52)]
Method of analysis	No formal sample size calculation was performed. The projected sample size of 750 direct-entry plus transferred-entry patients was considered adequate to obtain ≥ 300 patients who had received treatment with esketamine for 6 months, ≥ 100 patients for 12 months and ≥ 100 patients aged ≥ 65 years. Safety and efficacy outcomes were summarized descriptively. Furthermore, efficacy was analyzed using last-observation carried forward data and observed data.

Subgroup analyses	Patients were classified into subgroups based on age: <65 years and ≥ 65 years. Post-hoc analyses of SUSTAIN-2 based on MSM-scores was conducted to accommodate the Medicines Councils request for data on a sub-population with a MSM-score of ≥9.

Table A2.4a Baseline characteristics of SUSTAIN-2 (33, 34)

Characteristic	Esketamine Nasal Spray + OAD (N=802)
Age, y, mean (SD)	52.2 (13.69)
Age, y, n (%)	
18-44	225 (28.1)
45-64	399 (49.8)
65-74	159 (19.8)
≥ 75	19 (2.4)
Women, n (%)	502 (62.6)
Race, n (%)	
White	686 (85.5)
Asian	81 (10.1)
Black or African American	15 (1.9)
Other	8 (1.0)
Multiple	8 (1.0)
Not reported	4 (0.5)
Ethnicity, n (%)	
Not Hispanic or Latino	640 (79.8)
Hispanic or Latino	149 (18.6)
Not reported	10 (1.2)
Unknown	3 (0.4)
Baseline BMI, kg/m^2, mean (SD)	27.9 (5.68)
OAD, n (%)	
Duloxetine	251 (31.3)
Escitalopram	237 (29.6)
Sertraline	157 (19.6)
Venlafaxine XR	156 (19.5)
Baseline MADRS total score, mean (SD)	31.4 (5.39)
Baseline CGI-S score mean (SD)	4.8 (0.77)
History of suicidal ideation in the past 6 months, n (%)	215 (26.9)
Number of prior OAD with nonresponse in the current depressive episode, n (%)	
1	17 (2.1)
2	465 (58.0)
3	187 (23.3)
≥4	133 (16.6)
Family history of psychiatric illness, n (%)	
Depression	346 (43.1)
Anxiety disorder	61 (7.6)
Bipolar disorder	35 (4.4)
Schizophrenia	38 (4.7)

Table A2.5 Main study characteristics of SUSTAIN-3 (24, 25)

Trial name	SUSTAIN-3
NCT number	NCT02782104
Objective	The primary objective of SUSTAIN-3 was to assess the long-term safety of esketamine in conjunction with oral ADs in patients with TRD
Publications – title, author, journal, year	Janssen Research & Development L. Abbreviated Interim #2 Clinical Study Report - An Open-label Long-term Extension Safety Study of Esketamine Nasal Spray in Treatment resistant Depression - Safety and Sustenance of Esketamine Treatment Response with Repeated Doses at Intervals Determined by Symptom Severity (SUSTAIN-3). 2020.
Study type and design	SUSTAIN-3 is an ongoing phase III, multicenter, open-label, long-term extension study to evaluate the safety, tolerability, and efficacy or esketamine nasal spray in patients with TRD
[redacted]	
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Based on the prior study the participant is entering SUSTAIN-3 from: a) From TRANSFORM-1 (NCT02417064) or TRANSFOMR-2 (NCT02418585) study: Participant has completed the induction phase and the 2-weeks follow up phase visit; or Participants completed the induction phase and was a responder and study SUSTAIN-1 is terminated.; b) From SUSTAIn-1 (NCT02493868) study: (1) Participant relapsed during the maintenance phase; or (2) Participant was in the induction phase of the SUSTAIN-1 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or (3) Participant was in the optimization or maintenance phases at the time the study was terminated; or (4) or (5) Participants was in the induction phase and after completion of induction phase was determined to not meet response criteria (1) Participant completed SUSTAIN-2 study (optimization/maintenance phase); or (2) Participant was in the induction phase of the SUSTAIN-2 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or (3) Participant was in the optimization/maintenance phase at the time the study was terminated; (4) Participant was in the induction phase and did not meet criteria for response may be eligible for to be rolled over into SUSTAIN-3. d) From TRANSFORM-3 (NCT02422186) study: Participant was in the induction phase of the TRANSFORM-3 study at the time enrollment into the SUSTAIN-2 study was closed and, after completion of the induction phase, was determined to be a responder or did not meet the criteria for response. e) From ESKETINTRD3006 study (US Study sites only) (1) Participant completed the induction phase and was a responder.

	• Participant must be medically stable on the basis of physical examination, vital signs, pulse oximetry, and 12-lead Electrocardiogram (ECG) performed predose on the day of the first intranasal treatment session. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the participant's source documents and initialed by the investigator • Participant must be medically stable according to the investigator's judgment and knowledge of the subject's medical stability in the parent study. This determination must be documented. • A woman of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [b-hCG]) predose on the day of the first intranasal treatment session • During the study (that is, from the first intranasal treatment session) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential must be practicing a highly effective method of contraception with his female partner c) must agree not to donate sperm. Exclusion Criteria: • The evaluation of the benefit versus risk of continued esketamine nasal spray treatment is not favorable for the participant in the opinion of the investigator • Since the last study visit in the participant's prior study, participant has suicidal ideation with intent to act per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS) [corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) in the suicidal ideation module of the C-SSRS] or suicidal behavior per the investigator's clinical judgment or based on the C-SSRS (corresponding to any score higher than 0 in the suicidal behavior module of the C-SSRS) • Participant has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) predose on the day of the first intranasal treatment session • Participant has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of intranasal study drug • Participant has taken any prohibited therapies that would not permit administration of the first intranasal treatment session
Intervention	Open-Label Induction Phase: Participants will self-administer with esketamine nasal spray twice per week for 4 weeks as a flexible dose regimen (56 milligram [mg] or 84 mg for those < 65 years; 28 mg, 56 mg or 84 mg for those >= 65 years). Participants >= 65 years old will start at a dose of 28 mg on Day 1. Optimization/Maintenance Phase: Participants entering from studies TRANSFORM-1 (NCT02417064), TRANSFORM-2 (NCT02418585) or ESKETINTRD3006 (US sites only) will self-administer esketamine nasal spray (same dose) once weekly. Participants entering from study TRANSFORM-3

	(NCT02422186) will self-administer esketamine nasal spray (28 mg in week 1; 28 or 56 mg in week 2; and 28, 56 or 84 mg in week 3 and 4) once weekly. After Week 4 (starting at Week 5), based on the Investigator's clinical judgment, the dose of esketamine for all participants can be adjusted based upon efficacy and tolerability.
Baseline characteristics	*See table A2.5a*
Primary and secondary endpoints	Primary endpoints • Number of Participants With Treatment Emergent Adverse Events (TEAEs) [Time Frame: Up to End of Study (approximately 5 years 3 months)] • Change From Baseline in Systolic and Diastolic Blood Pressure [Time Frame: Baseline of each dosing session (predose) up to the last post-dose measurement from the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Heart Rate [Time Frame: Baseline of each dosing session (predose) up to the last post-dose measurement from the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Blood Oxygen Saturation [Time Frame: Baseline of each dosing session (predose) up to the last post-dose measurement from the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Modified Observer's Assessment of Alertness/Sedation (MOAAS) Scale Score [Time Frame: 1 hour post-dose from the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change from Baseline in Electrocardiogram (ECG) intervals [Time Frame: Baseline of each dosing session (predose) up to the last post-dose measurement from the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Computerized Cognitive Battery Domain Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Changes From Baseline Over Time in Clinical Laboratory Tests [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Time to Discharge Readiness Using the Clinical Global Assessment of Discharge Readiness (CGADR) [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] Secondary endpoints

	• Change From Baseline in Participant-Reported Depressive Symptoms Using the Patient Health Questionnaire - 9 (PHQ-9) Total Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Clinical Global Impression-Severity (CGI-S) score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in days when participants assess disruption of (1) work/school, (2) social life, leisure activities, and (3) family life/home responsibilities as Assessed by the Sheehan Disability Scale (SDS) Total Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in days symptoms caused participants to miss school or work or were unable to carry out normal daily responsibilitieswhen participant lost from school or work as as Assessed by the Sheehan Disability Scale (SDS) [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in days when participant was underproductive as Assessed by the Sheehan Disability Scale (SDS) [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Participant-Reported Health-related Quality of Life as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L)) Valuation Index Score [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Participant-Reported Health Status as Assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale (VAS) [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)] • Change From Baseline in Participant- Reported Health Related Quality of Life Using the Quality of Life in Depression Scale (QLDS) [Time Frame: From the start of Induction Phase to End of Optimization/Maintenance Phase (approximately 5 years 3 months)]

[redacted]

[redacted]

Subgroup analyses	n/a

Table A2.5a Baseline characteristics of SUSTAIN-3 (24)

[redacted]

Table A2.6 Main study characteristics of SYNAPSE (26, 27)

Trial name	SYNAPSE

NCT number	NCT01998958
Objective	The purpose of this study is to assess the efficacy and dose response of intranasal esketamine (Panel A: 28 mg, 56 mg, and 84 mg and Panel B: 14 mg and 56 mg) compared with placebo in improving depressive symptoms in participants with treatment-resistant depression (TRD).
Publications – title, author, journal, year	Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA psychiatry. 2018;75(2):139-48.
Study type and design	SYNAPSE was a Phase IIa doubly-randomized, double-blind, placebo-controlled, multicenter study of esketamine nasal spray for the treatment of patients with moderate to severe MDD who failed to respond to at least 2 AD therapies during their current MDD episode (History of inadequate response to ≥2 ADs of which ≥1 AD was used in the current episode of depression). It should be noted that this inclusion criteria differs from the TRD definition as well as the population studied in the Phase III trial
Follow-up time	All patients were entered into an 8-week follow-up phase regardless of their inclusion in the open-label phase
Population (inclusion and exclusion criteria)	Inclusion Criteria: --Participant must meet Diagnostic and Statistical Manual of Mental Disorders -Fourth Edition -Text Revised (DSM-IV-TR) diagnostic criteria for Major Depressive Disorder (MDD), without psychotic features, based upon clinical assessment, and confirmed by the Mini International Neuropsychiatric Interview (MINI)-Participant's major depressive episode and treatment response must be deemed "valid" by remote independent raters-Participant must have had an inadequate response to at least 2 antidepressants, at least one of which is in the current episode of depression; the antidepressant treatment response questionnaire (ATRQ) will be used to assess antidepressant treatment response during the current episode; prior medication history will be used to determine antidepressant treatment response in prior episode(s) -Have an Inventory of Depressive Symptoms-Clinician rated, 30-item (IDS-C30) total score >=34 at Screening and predose at Day 1 Exclusion Criteria: -Participant has a current DSM-IV-TR diagnosis of bipolar and related disorders, intellectual disability, or cluster b personality disorder (e.g., borderline personality disorder, antisocial personality disorder, histrionic personality disorder, and narcissistic personality disorder) -Participant has a current or prior DSM-IV-TR diagnosis of a psychotic disorder, MDD with psychosis, post-traumatic stress disorder (PTSD), or obsessive compulsive disorder (OCD) -Anatomical or medical conditions that may impede delivery or absorption of study medication (e.g., undergone facial reconstruction, rhinoplasty, significant structural or functional abnormalities of the nose or upper airway; obstructions or mucosal lesions of the nostrils or nasal passages; undergone sinus surgery in the previous 2 years; signs and symptoms of rhinitis) -Has an abnormal or deviated nasal septum with any 1 or more of the following symptoms: blockage of 1 or both nostrils, nasal congestion (especially 1-sided), frequent nosebleeds, frequent sinus infections, and at times has facial pain, headaches, and postnasal drip -Has a history of substance abuse (drug or alcohol) or dependence (except nicotine or caffeine) within the previous 1 year of the screening visit -Participant has known allergies, hypersensitivity, intolerance, or contraindication to esketamine/ketamine or its excipients

Intervention	• Drug: Esketamine 14 mg 1 to 6 sprays of esketamine 14 mg self-administered as an intranasal formulation for 4 days (Days 1, 4, 8, 11) during the double-blind phase and if applicable during the optional open-label phase for up to 4 days • Drug: Esketamine 28 mg 1 to 6 sprays of esketamine 28 mg self-administered as an intranasal formulation for 4 days (Days 1,4, 8, 11) during the double-blind phase and if applicable, during the optional open-label phase for up to 9 days • Drug: Esketamine 56 mg 1 to 6 sprays of esketamine 56 mg self-administered as an intranasal formulation for up to 4 days (Days 1, 4, 8, 11) during the double-blind phase and if applicable, during the optional open-label phase for up to 9 days • Drug: Esketamine 84 mg 1 to 6 sprays of esketamine 84 mg self-administered as an intranasal formulation for up to 4 days (Days 1, 4, 8, 11) during the double-blind phase and if applicable, during the optional open-label phase for up to 9 days • Drug: Placebo 1 to 6 sprays of placebo self-administered as an intranasal formulation for 2 days (Days 1 and 4) or depending on response on Day 8, for 4 days (Days 1,4, 8, 11) during the double-blind phase
Baseline characteristics	*See table A2.6a*
Primary and secondary endpoints	Primary endpoints • Panel A and B: Change From Baseline (Day 1) in Montgomery Asberg Depression Rating Scale (MADRS) Total Score at Day 8- Analysis of Covariance (ANCOVA) Analysis [Time Frame: Baseline (Day 1) and Endpoint (Day 8) of Period 1] • Panel A and B: Change From Baseline (Day 8) in Montgomery Asberg Depression Rating Scale Total Score at Day 15- ANCOVA Analysis [Time Frame: Baseline (Day 8) and Endpoint (Day 15) of Period 2] Secondary endpoints • Panel A and B: Percentage of Participants With Sustained Response Based on MADRS Total Score in Participants Who Have Completed the Double-Blind Phase and Received the Same Treatment for Both Periods [Time Frame: Day 2 Up to Day 15] • Panel A and B: Percentage of Participants With Sustained Response Based on MADRS Total Score in Participants Who Received the Same Treatment for Both Periods, Including Participants Who Did Not Complete the Double-blind Phase [Time Frame: Day 2 Up to Day 15]

	• Panel A and B: Percentage of Participants With Response Based on MADRS Total Score [Time Frame: Period 1: Days 1 (2 hour), 2 and 8 of Double-blind Phase] • Panel A and B: Percentage of Participants With Response Based on MADRS Total Score [Time Frame: Period 2: Days 1 (2 hour), 2 and 8 of Double-blind Phase] • Panel A and B: Percentage of Participants in Remission Based on MADRS Total Score at Days 1, 2 and 8 of Double-blind Phase [Time Frame: Days 1, 2 and 8 of Double-blind Phase of Period 1] • Panel A and B: Percentage of Participants in Remission Based on MADRS Total Score at Days 1, 2 and 8 of Double-blind Phase [Time Frame: Days 1, 2 and 8 of Double-blind Phase of Period 2] • Panel A and B: Change From Baseline (Day 1) in Quick Inventory of Depressive Symptomatology-16-item Self Report (QIDS-SR16) Total Score at Day 8 in the Double-Blind Treatment Phase- ANCOVA Analysis [Time Frame: Baseline (Day 1) and Endpoint (Day 8) of Period 1] • Panel A and B: Change From Baseline (Day 8) in Quick Inventory of Depressive Symptomatology-16-item Self Report Total Score at Day 15 in the Double-Blind Treatment Phase- ANCOVA Analysis [Time Frame: Baseline (Day 8) and Endpoint (Day 15) of Period 2] • Panel A and B: Change From Baseline (Day 1) in Clinical Global Impression - Severity (CGI-S) Total Score at Day 8 in the Double-Blind Treatment Phase- ANCOVA Analysis on Ranks [Time Frame: Baseline (Day 1) and Endpoint (Day 8) of Period 1] • Panel A and B: Change From Baseline (Day 8) in Clinical Global Impression - Severity Total Score at Day 15 in the Double-Blind Treatment Phase- ANCOVA Analysis on Ranks [Time Frame: Baseline (Day 8) and Endpoint (Day 15) of Period 2] • Panel A and B: Change From Baseline (Day 1) in Generalized Anxiety Disorder (GAD-7) Total Score at Day 8 (Double-Blind Treatment Phase) ANCOVA Analysis [Time Frame: Baseline (Day 1) and Endpoint (Day 8) of Period 1] • Panel A and B: Change From Baseline (Day 8) in Generalized Anxiety Disorder-7 Total Score at Day 15 (Double-Blind Treatment Phase)-ANCOVA Analysis [Time Frame: Baseline (Day 8) and Endpoint (Day 15) of Period 2] • Panel A and B: Change From Baseline (Day 1) in Patient Global Impression of Severity (PGI-S) Score Total Score at Day 8 in the Double-Blind Treatment Phase- ANCOVA Analysis on Ranks [Time Frame: Baseline (Day 1) and Endpoint (Day 8) of Period 1] • Panel A and B: Change From Baseline (Day 8) in Patient Global Impression of Severity Score Total Score at Day 15 in the Double-Blind Treatment Phase- ANCOVA Analysis on Ranks [Time Frame: Baseline (Day 8) and Endpoint (Day 15) of Period 2]
Method of analysis	Efficacy datawere analyzed in intent-to-treat analysis sets for each period and phase

Subgroup analyses	n/a

Table A2.6a Baseline characteristics of SYNAPSE (26)

		Esketamine			
Parameter	Placebo (N=33)	28mg (N=11)	56mg (N=11)	84mg (N=12)	Total (N=67)
Age, years Mean (SD)	44.4 (9.60)	42.1 (10.31)	42.7 (11.23)	49.8 (9.29)	44.7 (10.04)
Sex, n (%) Female	18 (54.5)	5 (45.5)	9 (81.8)	6 (50.0)	38 (56.7)
Race, n (%) White Black or African American American Indian or Alaska native	24 (72.7) 9 (27.3) 0	7 (63.6) 4 (36.4) 0	6 (54.5) 4 (36.4) 1 (9.1)	11 (91.7) 1 (8.3) 0	48 (71.6) 18 (26.9) 1 (1.5)
BMI, kg/m2 Mean (SD)	29.7 (6.00)	29.0 (6.18)	30.1 (8.30)	30.4 (8.47)	29.8 (6.77)
MADRS Total Score Mean (SD)	35.0 (5.18)	31.3 (3.80)	33.2 (6.26)	35.0 (4.22)	34.1 (5.11)
Duration of Current Episode (wks) Mean (SD)	65.2 (79.93)	56.1 (39.28)	39.9 (21.82)	66.6 (51.54)	59.8 (63.5)
Number of Major Depressive Episodes < 3 ≥ 3	4 (12.1)	3 (33.3)	2 (20.0)	2 (18.2)	11 (17.5)
Number of Antidepressants in Current Episode of Major Depression 1 2 ≥ 3	21 (63.6) 7 (21.2) 5 (15.2)	6 (54.5) 4 (36.4) 1 (9.1)	8 (72.7) 2 (18.2) 1 (9.1)	8 (66.7) 2 (16.7) 2 (16.7)	43 (64.2) 15 (22.4) 9 (13.4)

Abbreviations: BMI = body mass index; MADRS = Montgomery-Asberg Depression Rating Scale; SD = standard deviation

Table A2.7 Main study characteristics of ATU (28)

Trial name	Cohort Authorization for Temporary Use - ESKETAMINE JANSSEN 28 mg, nasal spray
NCT number	n/a
Objective	The objective of this study it to describe socio-demographic, clinical characteristics and pharmacovigilance data for the TRD patients enrolled in the ATUc
Publications – title, author, journal, year	Janssen-Cilag. Cohort Authorization for Temporary Use, ESKETAMINE JANSSEN 28 mg, nasal spray. Final Report: Complete report on cumulative period from 23/09/2019 to 25/03/2020. 2020.
Study type and design	This is a non-interventional observational prospective cohort study of TRD patients treated with esketamine under real-life clinical routine practice.
Follow-up time	n/a
Population (inclusion and exclusion criteria)	The eligibility criteria of the cohort ATU were as follows: • Male or Female older than 18 years old • Patient with moderate to severe depression based on clinical judgement • Patient with a diagnosis of treatment-resistant depression without other therapeutic alternatives: o Meeting the DSM-5 diagnostic criteria for a single episode of major depression (if it is a single episode, the duration must be at least 2 years) or a recurrent episode with no psychotic features o Non-response to at least two different classes of antidepressant medications during the current depressive episode confirmed by medical history and have a contraindication to electroconvulsive therapy (ECT), be resistant to ECT, no access to ECT or refuse ECT • Patient medically stable based on physical examination, medical history and vital signs (including stable blood pressure) • Not being able to take part of a clinical trial • Before starting treatment, women of childbearing potential should use a highly effective method of contraception and agree to continue to use it for the duration of the ATU and for at least six weeks after the last dose of esketamine
Intervention	The eligible patients received esketamine according to the Summary of Product Characteristics
Baseline characteristics	*See table A2.7a*
Primary and secondary endpoints	n/a
Method of analysis	Quantitative variables will be summarized using descriptive statistical methods (mean, standard deviation, median, minimum and maximum)
Subgroup analyses	n/a

Table A2.7a Baseline characteristics of ATU (28)

Parameter	Patients treated (N=66)
Age, years, mean (SD)	52.5 (16.7)
Female, n (%)	41 (62.1)
Duration of illness, years, mean (SD)	16.5 (14.4)
Duration of the current depressive episode, years, mean (SD)[a]	3.5 (2.5)
Severity of current depressive episode, n (%)	
Moderate	14 (21.2)
Severe	52 (78.8)
MADRS total score, mean (SD)[b]	31.7 (5.9)
Blood pressure, mmHg, mean (SD)	
Systolic	124.7 (14.3)
Diastolic	76.2 (9.4)
Treatments prescribed since the start of the current depressive episode, n (%)	
Antidepressant(s)	66 (100)
Antipsychotic	54 (81.8)
ECT	28 (42.4)
rTMS	21 (31.8)

[a]n=23 (data collected from December 2019)

[b]n=63

Abbreviations: ECT, Electroconvulsive therapy; MADRS, Montgomery – Åsberg Depression Rati ng Scale; rTMS, repetitive transcranial magnetic stimulation; SD, Standard deviation

Table A2.8 Main study characteristics of TRD cohort study (29, 30)

Trial name	Treatment-resistant depression cohort I Europe
NCT number	NCT03373253
Objective	The purpose of this study is to assess the participants socio-demographics and disease-related characteristics, long-term naturalistic treatment patterns and the clinical, social and economic outcomes of routine clinical practice in the treatment of participants with treatment-resistant depression (TRD) in a variety of European countries.
Publications – title, author, journal, year	Heerlein K, Young AH, Otte C, Frodl T, Degraeve G, Hagedoorn W, et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: Baseline patient characteristics. Journal of affective disorders. 2021;283:115-22
Study type and design	This is a observational prospective cohort study of TRD patients treated under real-life clinical routine practice.
Follow-up time	21 months was the maximum time enrolled in the study for any individual patient; all patients had a minimum of 6 months follow-up.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Meets the diagnostic criteria for single episode or recurrent MDD, without psychotic features, according to either the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) • Is considered to suffer from a moderate or severe depressive syndrome, as defined by a Montgomery-Asberg Depression Rating Scale (MADRS) total score greater than or equal to (>=) 20 at baseline • Meets/has met the TRD criteria, defined as lack of clinically meaningful improvement, as indicated by a Clinical Global Impression-Change (CGI-C) score >= 4 and/or less than or equal to (<=) 25 percent (%) improvement in MADRS total score (lack of tolerability is not an indicator of non-response), with at least 2 different oral antidepressant treatments (of the same class, of a different class, or a combination of antidepressants or antidepressant with adjunctive antipsychotics) in the current episode of depression, prescribed in adequate dosages (as defined in the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire [MGH ATRQ]) for adequate duration (at least 6 weeks) with adequate treatment adherence assessed by physicians • Is initiating a new antidepressive treatment to treat the current depressive episode • Must be capable of providing informed consent, based on the opinion of the participating physician Exclusion Criteria: • Has a current or prior diagnosis of a psychotic disorder, MDD with psychotic features, bipolar or related disorders, or intellectual disability, according to DSM-5 or ICD-10 • Has homicidal ideation/intent or has suicidal ideation with some intent to act, within 1 month prior to enrollment (per the physician's clinical judgment or

	based on the Columbia-Suicide Severity Rating Scale [C-SSRS] corresponding to a response of "Yes" on Item 4 [active suicidal ideation with some intent to act, without specific plan] or Item 5 [active suicidal ideation with specific plan and intent]) or a history of suicidal behavior within 1 year prior to enrollment • Has a history of moderate or severe substance use disorder or severe alcohol use disorder according to DSM 5 criteria, except for nicotine and caffeine, within 6 months prior to enrollment • Has a lifetime history of hallucinogen-related substance use disorder, with ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), or 3,4 methylenedioxy-methamphetamine (MDMA) • Has participated in or is currently enrolled in any clinical trial or observational study within the current episode • Has previously received esketamine at any time
Intervention	All patients were initiating a new antidepressant treatment according to standard care in their treatment setting, with choice of treatment, and dose and administration (if applicable) at the discretion of the prescribing clinician.
Baseline characteristics	*See table A2.8a*
Primary and secondary endpoints	Primary endpoints • Number of Treatment Resistant Depression (TRD) Participants With Change From Baseline in Socio-demographic Characteristics [Time Frame: Baseline up to 21 months (end of study)] • Treatment Patterns Over Time for TRD Participants [Time Frame: Baseline up to 21 months (end of study)] • Percentage of Participants With Disease-Related Characteristics [Time Frame: Up to 21 months] • Severity of Symptoms as Measured by Montgomery-Asberg Depression Rating Scale (MADRS) [Time Frame: Up to 21 months] • Participant's Clinical Global Impression-Severity (CGI-S) Score [Time Frame: Up to 21 months] • Participant's Clinical Global Impression-Change Scale (CGI-C) [Time Frame: Up to 21 months] • Healthcare Resource Utilization in TRD Participants [Time Frame: Up to 21 months] • European Quality of Life (EuroQol) 5-Dimension 5-Level Questionnaire [Time Frame: Up to 21 months] • Quality of Life in Depression Scale (QLDS) [Time Frame: Up to 21 months] • Work Productivity and Activity Impairment (WPAI) [Time Frame: Up to 21 months] • Level of Disability as Sheehan Disability Scale (SDS) [Time Frame: Up to 21 months]

	• Sequence of Treatments in Participants with TRD [Time Frame: Up to 21 months] • Demographic Characteristics of TRD Participants [Time Frame: Baseline] • Suicidality Risk (Ideation and Attempts) as Measured by Columbia-Suicide Severity Rating Scale (C-SSRS) Score [Time Frame: Baseline]
Method of analysis	Analyses were carried out on the data from the final data cut taken 30 March 2020. Descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) were used to summarize continuous variables. Frequency distribution (number and percentage of patients in each category) was used to summarize categorical variables.
Subgroup analyses	n/a

Table A2.8a Baseline characteristics of TRD cohort study (29, 30)

Category	N=411
Clinical evaluation at baseline	
Total MADRS score, mean (SD)	31.8 (6.0)
Disease severity, MADRS category, n (%) Moderate depression Severe depression	 277 (67.4) 134 (32.6)
Disease change*, CGI-C, n (%) No change Minimally worse Much/very much worse	 267 (65.0) 83 (20.2) 61 (14.8)
Psychiatric and medical history	
Age (years) at diagnosis with MDD, mean (SD)	37.2 (13.1)
Years since diagnosed with MDD, mean (SD)	13.7 (11.2)
Duration of current MDE in weeks, mean (SD)	136.3 (203.8)
First or recurrent episode, n** (%) First episode Recurrent episode	 93 (22.6) 310 (75.4)
Previous depressive episodes, mean (SD)	3.4 (5.6)

*Relative to assessments carried out at the time point the previous treatment was initiated. **Data only obtained for 403 patients; no data were obtained from 8 patients. CGI-C: Clinical Global Impression of Change; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; SD: standard deviation.

8.2 Results per study

Table A3a Results of the TRANSFORM-1 study

Trial name:	*TRANSFORM-1*					
NCT number:	NCT02417064					
	Data extracted from TRANSFORM-1			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	Pooled ESK-NS 56-84 mg + OAD	2/231	1.7%	2.457*	0.12-50.75*	*Data extracted as stated in the study or EPAR for the full TRD population. Relative difference is provided as unadjusted risk ratio.* *Data for the MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9 populations are based on post-hoc analyses of the TRANSFORM-1 study after applying the Maudsley Staging Method to identify patients in each of the groups. Relative difference is provided as unadjusted risk ratio.* **In TRANSFORM-1, there is no SAE in the OAD+PBO arm, meaning a probability of 0, and then a non-computable relative risk (divide by 0). Consequently, classical approach with adding 0.5 subject to those having outcome and 0.5 to those not having an outcome given an extra fictional participant in both treatment arms was conducted.*
	OAD+PBO	0/113	0%			
Discontinuation due to adverse events	Pooled ESK-NS 56-84 mg + OAD	8/231	3.5%	1.957	0.442-9.064	
	OAD+PBO	2/113	1.8%			
Response full TRD population	Pooled ESK-NS 56-84 mg + OAD	112/209	53.5%	1.378	1.054-1.801	
	OAD+PBO	42/108	38.9%			
Response MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			

Remission full TRD population	Pooled ESK-NS 56-84 mg + OAD	78/209	37.3%	1.221	0.874-1.706	
	OAD+PBO	33/108	30.5%			
Remission MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
EQ-5D-5L	ESK-NS 56 mg + OAD	113	0.224 (SD;0.248)	0.043**	-0.022-0.108**	**Unpublished post-hoc analysis of mean difference pooled (56mg + 84mg) results for study TRANSFORM-1 on EQ-5D-5L.* ***No relative difference in effect reported but the mean difference change in health status index.*
	ESK-NS 84 mg + OAD	112	0.243 (SD;0.239)	0.062**	-0.002-0.126**	
	Pooled ESK-NS 56-84 + OAD	225*	0.233(SD: 0.244)*	0.052**	-0.004-0.108**	
	OAD+PBO	113	0.181 (SD;0.249)	n/a	n/a	

Table A3b Results of the TRANSFORM-2 study

Trial name:	*TRANSFORM-2*					
NCT number:	NCT02418585					
	Data extracted from TRANSFORM-2			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	ESK-NS 56-84 mg + OAD	1/115	0.9%	0.948	0.060-14.966	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.* *Data for the MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9 populations are based on post-hoc analyses of the TRANSFORM-2 study after applying the Maudsley Staging Method to identify patients in each of the groups. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO-NS	1/109	0.9%			
Discontinuation due to adverse events	ESK-NS 56-84 mg + OAD	8/115	7%	7.583	0.964-59.629	
	OAD+PBO-NS	1/109	0.9%			
Response full TRD population	ESK-NS 56-84 mg + OAD	70/101	69.3%	1.333	1.060-1.675	
	OAD+PBO-NS	52/100	52%			
Response MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			

Remission full TRD population	ESK-NS 56-84 mg + OAD	53/101	52.5%	1.693	1.197-2.393	
	OAD+PBO-NS	31/100	31%			
Remission MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
EQ-5D-5L	ESK-NS 56-84 mg + OAD	114	0.288 (SD;0.2317)	0.057*	-0.007-0.121*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO-NS	109	0.231 (SD;0.2506)			

Table A3c Results of the TRANSFORM-3 study

Trial name:	*TRANSFORM-3*					
NCT number:	NCT02422186					
	Data extracted from TRANSFORM-3			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	Pooled ESK-NS 28-56-84 mg + OAD	3/72	4.2%	1.354	0.234-7.851	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.* *Data for the MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9 populations are based on post-hoc analyses of the TRANSFORM-3 study after applying the Maudsley Staging Method to identify patients in each of the groups. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO-NS	2/65	3.1%			
Discontinuation due to adverse events	Pooled ESK-NS 28-56-84 mg + OAD	4/72	5.6%	1.806	0.342-9.534	
	OAD+PBO-NS	2/65	3.1%			
Response full TRD population	Pooled ESK-NS 28-56-84 mg + OAD	17/63	27%	2.024	0.944-4.338	
	OAD+PBO-NS	8/60	13.3%			
Response MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Response MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			

Remission full TRD population	Pooled ESK-NS 28-56-84 mg + OAD	11/63	17.5%	2.619	0.882-7.777	
	OAD+PBO-NS	4/60	6.7%			
Remission MSM ≥ 7 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 8 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
Remission MSM ≥ 9 Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]			
EQ-5D-5L	Pooled ESK-NS 28-56-84 mg + OAD	70	0.081 (SD;0.2624)	0.055*	-0.027-0.137*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO-NS	64	0.026 (SD;0.2235)			

Table A3d Results of the SUSTAIN-1 study

Trial name:	*SUSTAIN-1*					
NCT number:	NCT02417064					
	Data extracted from SUSTAIN-1			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
*Serious adverse events**	Pooled ESK-NS 56-84 mg + OAD	4/152	2.6%	3.816	0.432-33.739	*Data extracted as stated in the study or EPAR. Relative difference is provided as unadjusted risk ratio.*
	OAD+PBO-NS	1/145	0.7%			
*Discontinuation due to adverse events**	Pooled ESK-NS 56-84 mg + OAD	4/152	2.6%	1.272	0.290-5.585	
	OAD+PBO-NS	3/145	2.1%			
Response - stable remitters	Pooled ESK-NS 56-84 mg + OAD	67/89	75.3%	1.349	1.080-1.685	
	OAD+PBO-NS	48/86	55.8%			
Response - stable responders	Pooled ESK-NS 56-84 mg + OAD	41/62	66.1%	1.951	1.310-2.906	
	OAD+PBO-NS	20/59	33.9%			
Remission - stable remitters	Pooled ESK-NS 56-84 mg + OAD	58/89	65.2%	1.557	1.163-2.084	
	OAD+PBO-NS	36/86	41.9%			

Remission - stable responders	Pooled ESK-NS 56-84 mg + OAD	29/62	46.8%	1.840	1.103-3.068	
	OAD+PBO-NS	15/59	25.4%			
EQ-5D-5L among stable remitters	Pooled ESK-NS 56-84 mg + OAD	88	-0.067 (SD;0.1180)	0.029*	-0.011-0.069*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO-NS	86	-0.096 (SD;0.1484)			
EQ-5D-5L among stable responders	Pooled ESK-NS 56-84 mg + OAD	61	-0.023 (SD;0.0753)	0.050*	0.010-0.090*	**No relative difference in effect reported but the mean difference change in health status index.*
	OAD+PBO-NS	58	-0.073 (SD;0.1383)			

Table A3e Results of the SUSTAIN-2 study

Trial name:	*SUSTAIN-2*					
NCT number:	NCT02497287					
	Data extracted from SUTAIN-2			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	ESK-NS + OAD	55/802	6.9%	-	-	Safety analyses were summarized for the entire treatment period based on the all enrolled analysis set (all patients who were not screen failures and received ≥ 1 dose of esketamine or 1 dose of OAD.
Discontinuation due to adverse events	ESK-NS + OAD	76/802	9.5%	-	-	
Response at end of induction	ESK-NS + OAD	593/756	78.4%	-	-	Results presented as stated in the SUSTAIN-2 article. Efficacy was analyzed using last-observation carried forward data.
Response at end of optimization/ maintenance	ESK-NS + OAD	461/603	76.5%	-	-	
Remission at end of induction	ESK-NS + OAD	357/756	47.2%	-	-	
Remission at end of optimization/ maintenance	ESK-NS + OAD	351/603	58.2%	-	-	
Response at 6 months full TRD population	[redacted]	[redacted]	[redacted]	-	-	Methodology of the post-hoc analyses on efficacy outcomes from SUSTAIN-2 at 6 months are available in section 8.5.1.

Response at 6 months MSM ≥ 7 Population				-	-	
Response at 6 months MSM ≥ 8 Population				-	-	
Response at 6 months MSM ≥ 9 Population				-	-	
Remission at 6 months full TRD population				-	-	
Remission at 6 months MSM ≥ 7 Population				-	-	
Remission at 6 months MSM ≥ 8 Population				-	-	
Remission at 6 months MSM ≥ 9 Population				-	-	
EQ-5D-5L full TRD population at end of induction				-	-	Results presented as stated in the SUSTAIN-2 article Efficacy was analyzed using last-observation carried forward data.
EQ-5D-5L full TRD population				-	-	

from baseline (OP/MA) to end of OP/MA						

Table A3f Results of the SUSTAIN-3 study

Trial name:	*SUSTAIN-3*					
NCT number:	NCT02782104					
	Data extracted from SUSTAIN-3			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	[redacted]	[redacted]	[redacted]	-	-	Results for subjects in the all enrolled analysis set (induction plus optimization/maintenance phases)
Discontinuation due to adverse events	[redacted]	[redacted]	[redacted]	-	-	Results for subjects in the all enrolled analysis set (induction plus optimization/maintenance phases)
Response	ESK-NS + OAD	-	-	-	-	Efficacy data response is not reported in the open-label long-term extension safety study of esketamine nasal spray in treatment resistant depression (SUSTAIN-3)
Remission	ESK-NS + OAD	-	-	-	-	Efficacy data on remission is not reported in the open-label long-term extension safety study of esketamine nasal spray in treatment resistant depression (SUSTAIN-3)
EQ-5D-5L	ESK-NS + OAD	-	-	-	-	Efficacy data on EQ-5D-5L HSI is not reported in the open-label long-term extension safety study of esketamine nasal spray in treatment resistant depression (SUSTAIN-3).

Table A3g Results of the SYNAPSE study

Trial name:	*SYNAPSE*					
NCT number:	NCT01998958					
	Data extracted from SYNAPSE			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	ESK-NS 28 mg	0/11*	0%*	-	-	* Data reported for panel A in period 1 ** Data reported for panel A in period 2 *No relative difference is provided as the rate of SAE is 0% in both the ESK-NS 28 mg arm and the PBO-NS arm*
		0/16**	0%**			
	ESK-NS 56 mg	0/20*	0%*	-	-	*Data reported for both panel A and panel B in period 1 as stratified data on panel A and panel B is not reported **Data reported for both panel A and panel B in period 2 as stratified data on panel A and panel B is not reported *No relative difference is provided as the rate of SAE is 0% in both the ESK-NS 28 mg arm and the PBO-NS arm*
		0/32**	0%**			
	ESK-NS 84 mg	0/12*	0%*	-	-	* Data reported for panel A in period 1 ** Data reported for panel A in period 2 *No relative difference is provided as the rate of SAE is 0% in both the ESK-NS 28 mg arm and the PBO-NS arm*
		0/17**	0%**			
	PBO-NS*	0/54	0%	-	-	* Data reported for both panel A and panel B for period 1 as stratified data on panel A and panel B is not reported
Discontinuation due to adverse events	Pooled ESK-NS 28-56-84 mg	3/56*	5.4%	X**	X-X**	* Patients during the double-blind phase ** In SYNAPSE, there is no discontinuation due to AE in the PBO-NS arm, meaning a probability of 0, and then a non-computable relative risk (divide by 0). Consequently, classical approach with adding 0.5 subject to those having outcome and 0.5 to those not having an outcome given an extra fictional participant in both treatment arms was conducted.
	PBO-NS	0/33	0%			
Response	ESK-NS 28 mg	3/8	37.5%	3.750	0.476-29.524	

	ESK-NS 56 mg	4/11	36.4%	3.636	0.484-27.332	*Data extracted as stated in the SYNAPSE study. Relative difference is provided as unadjusted risk ratio.*
	ESK-NS 84 mg	5/10	50%	5.000	0.704-35.497	
	PBO-NS	1/10	10%	-	-	
Remission	ESK-NS 28 mg	1/8	12.5%	1.250	0.092-17.021	*Data extracted as stated in the SYNAPSE study. Relative difference is provided as unadjusted risk ratio.*
	ESK-NS 56 mg	3/11	27.7%	2.727	0.336-22.159	
	ESK-NS 84 mg	4/10	40%	4.000	0.537-29.806	
	PBO-NS	1/10	10%	-	-	
EQ-5D-5L	ESK-NS 28 mg	-	-	-	-	*No publicly available results on EQ-5D-5L for SYNAPSE*
	ESK-NS 56 mg	-	-	-	-	
	ESK-NS 84 mg	-	-	-	-	
	PBO-NS	-	-	-	-	

Table A3h Results of the ATU study

Trial name:	*ATU*					
NCT number:	*n/a*					
	Data extracted from ATU			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	ESK-NS + OAD	8/52	15.4%	-	-	*No comparative arm, thus relative differenced in effect is not reported.*
Discontinua-tion due to adverse events	ESK-NS + OAD	25/66	37.9%	-	-	*No comparative arm, thus relative differenced in effect is not reported.*
Response	ESK-NS + OAD	-	-	-	-	No publicly available evidence is available on response
Remission	ESK-NS + OAD	-	-	-	-	No publicly available evidence is available on remission
EQ-5D-5L	ESK-NS + OAD	-	-	-	-	No publicly available evidence is available on EQ-5D-5L

Table A3i Results of the TRD cohort study

Trial name:	*TRD cohort*					
NCT number:	NCT03373253					
	Data extracted from TRD cohort			Estimated relative difference in effect (risk ratio)		Description of methods used for estimation
Outcome	Study arm	n/N	Result	Difference	95% CI	
Serious adverse events	SOC	-	-	-	-	No evidence is available on serious adverse events
Discontinuation due to adverse events	SOC	-	-	-	-	No evidence is available on discontinuation due to adverse events
Response at 6 months full TRD population	SOC	[redacted]	[redacted]	-	-	Methodology of the post-hoc analyses on efficacy outcomes from the TRD cohort at 6 months are available in section 8.5.1. *Data for the MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9 populations are based on post-hoc analyses of the TRD cohort study after applying the Maudsley Staging Method to identify patients in each of the groups.* *No comparative arm, thus relative differenced in effect is not reported.*
Response at 6 months MSM ≥ 7 Population	SOC	[redacted]	[redacted]	-	-	
Response at 6 months MSM ≥ 8 Population	SOC	[redacted]	[redacted]	-	-	
Response at 6 months MSM ≥ 9 Population	SOC	[redacted]	[redacted]	-	-	
Remission at 6 months	SOC	[redacted]	[redacted]	-	-	

full TRD population						
Remission at 6 months MSM ≥ 7 Population	SOC	[redacted]	[redacted]	-	-	
Remission at 6 months MSM ≥ 8 Population	SOC	[redacted]	[redacted]	-	-	
Remission at 6 months MSM ≥ 9 Population	SOC	[redacted]	[redacted]	-	-	
EQ-5D-5L ***at 6 months***	SOC*	[redacted]	[redacted]	-	-	*Results presented as stated by Heerlein et al. 2021, thus patient population differs from the one included in the post-hoc analyses conducted by Janssen, see table 40 in section 6.1.11.* *Continuous variables were summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum).* **Results reported for patients with no response* ***Results reported for patients with response without remission (*response without remission: MADRS improvement from baseline ≥50% and MADRS score >10.) ****Results reported for patients with remission (*Remission: MADRS score ≤10)
	SOC**	[redacted]	[redacted]	-	-	
	SOC**	[redacted]	[redacted]	-	-	

Results per PICO

Table A4 Results referring to clinical question 1.

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Risk ratio	CI	*P* value	
Serious adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	0.4%	-0.7%-4.5%	n/a	1.398	0.369-5.295	0.622 No significant difference as indicated by the CI containing the value 1.	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was 1.0%*
	SUSTAIN-1	1.9%	-0.9%-4.8%	n/a	3.816	0.432-33.739	No significant difference as indicated by the CI containing the value 1.	*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*
Discontinuation due to adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	2.8%	-0.1%-10.4%	n/a	2.598	0.966-6.985	0.059 No significant difference as indicated	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.*

							by the CI containing the value 1.	*Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was 1.7%*
	SUSTAIN-1	0.6%	-2.9%-4.0%	n/a	1.272	0.290-5.585	No significant difference as indicated by the CI containing the value 1.	*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*
Response	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	14.4%	6.2%-24.1%	n/a	1.379	1.164-1.634	< 0.001	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was 38.1%*
	SUSTAIN-1 stable remitters	19.5%	5.7%-33.3%	n/a	1.349	1.080-1.685		*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*

	SUSTAIN-1 stable responders	32.2%	15.4%-49.1%	n/a	1.951	1.310-2.906		*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Results are based on the ITC of SUSTAIN-2 and the TRD cohort, for methodology see section 8.5.1. Furthermore,* RR were calculated based on the OR from the ITC. The absolute differences in effect were calculated using the estimated risk ratio (RR), the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies. *The event rate of the TRD cohort arm used to calculate the absolute difference was* [redacted]
Remission	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	11.9%	4.1%-21.8%	n/a	1.470	1.163-1.860	0.001	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using fixed effects inverse variance model.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* *The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was 25.4%*
	SUSTAIN-1 stable remitters	23.3%	8.9%-37.7%	n/a	1.557	1.163-2.084		*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*

	SUSTAIN-1 stable responders	21.4%	4.7%-38.0%	n/a	1.840	1.103-3.068		*Absolute difference in effect were calculated using the reported proportions having an event in the ESK-NS+OAD and OAD+PBO-NS arms. Relative difference provided as unadjusted risk ratio.*
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Results are based on the ITC of SUSTAIN-2 and the TRD cohort, for methodology see section 8.5.1. Furthermore,* RR were calculated based on the OR from the ITC. The absolute differences in effect were calculated using the estimated risk ratio (RR), the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies. *The event rate of the TRD cohort arm used to calculate the absolute difference was* [redacted]
EQ-5D-5L	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	0.054	0.017-0.092	0.004	n/a	n/a	n/a	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies using Continuous Fixed-Effect Model for the metric, mean difference.*
	SUSTAIN-1 stable remitters	0.029	-0.011-0.069		n/a	n/a	n/a	*Mean difference change in health status index among stable remitters*
	SUSTAIN-1 stable responders	0.050	0.010-0.090		n/a	n/a	n/a	*Mean difference change in health status index among stable responders*

Table A4.1 Results referring to clinical question 2.

Results per outcome	Studies included in the analysis	MSM score	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
			Difference	CI	*P* value	Risk ratio	CI	*P* value	
Serious adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3 SUSTAIN-1 SUSTAIN-2 SUSTAIN-3 ATU	MSM ≥ 7	-	-	-	-	-	-	*No comparative analyses for clinical question 2. Consequently, we refer to table A4 for results referring to clinical question 1 which is representative also for the subpopulation of patients with a MSM ≥ 7, MSM ≥ 8 or MSM ≥ 9 score.* *Furthermore, we refer to the safety results presented for each study in section 6.1 and the narrative review in section 6.1.12*
		MSM ≥ 8	-	-	-	-	-	-	
		MSM ≥ 9	-	-	-	-	-	-	
Discontinuation due to adverse events	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3 SUSTAIN-1 SUSTAIN-2 SUSTAIN-3 ATU	MSM ≥ 7	-	-	-	-	-	-	*No comparative analyses for clinical question 2. Consequently, we refer to table A4 for results referring to clinical question 1 which is representative also for the subpopulation of patients with a MSM ≥ 7, MSM ≥ 8 or MSM ≥ 9 score.* *Furthermore, we refer to the safety results presented for each study in section 6.1 and the narrative review in section 6.1.12*
		MSM ≥ 8	-	-	-	-	-	-	
		MSM ≥ 9	-	-	-	-	-	-	
Response	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	MSM ≥ 7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies. For the MSM ≥ 7 and MSM ≥ 8 subpopulation the meta-analyses was*

		MSM ≥ 8**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*conducted using fixed effects inverse variance model whereas a random effects model was used for the MSM ≥ 9 subpopulation.* *Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4.* **The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was [redacted]* ***The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was [redacted]* ****The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was [redacted]*
		MSM ≥ 9***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	SUSTAIN-2 & TRD cohort study	MSM ≥ 7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Results are based on the ITC of SUSTAIN-2 and the TRD cohort, for methodology see section 8.5.1. Furthermore,* RR were calculated based on the OR from the ITC. The absolute differences in effect were calculated using the estimated risk ratio (RR), the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies.
		MSM ≥ 8**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		MSM ≥ 9***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

									*The event rate of the TRD cohort arm used to calculate the absolute difference was [redacted] **The event rate of the TRD cohort arm used to calculate the absolute difference was [redacted] *** The event rate of the TRD cohort arm used to calculate the absolute difference was [redacted]
Remission	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	MSM ≥ 7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies. For the MSM ≥ 7 and MSM ≥ 8 subpopulation the meta-analyses was conducted using fixed effects inverse variance model whereas a random effects model was used for the MSM ≥ 9 subpopulation. Absolute difference in effect were calculated using the estimated risk ratio from the meta-analyses and the formula provided in the Handbook of the Medicines Council's process and methodologies version 2.4. *The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was [redacted] **The event rate of the OAD+PBO-NS arm based on the meta-analysis used to calculate the absolute difference was [redacted] ***The event rate of the OAD+PBO-NS arm based on the meta-analysis used
		MSM ≥ 8**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		MSM ≥ 9***	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

									to calculate the absolute difference was [redacted]
	SUSTAIN-2 & TRD cohort study	MSM ≥ 7*	[redacted]						*Results are based on the ITC of SUSTAIN-2 and the TRD cohort, for methodology see section 8.5.1. Furthermore,* RR were calculated based on the OR from the ITC. The absolute differences in effect were calculated using the estimated risk ratio (RR), the event rates and the formula provided in the Handbook of the Medicines Council's process and methodologies. **The event rate of the TRD cohort arm used to calculate the absolute difference was* [redacted] ***The event rate of the TRD cohort arm used to calculate the absolute difference was* [redacted] **** The event rate of the TRD cohort arm used to calculate the absolute difference was* [redacted]
		MSM ≥ 8**							
		MSM ≥ 9***							
EQ-5D-5L	TRANSFORM-1 TRANSFORM-2 TRANSFORM-3	MSM ≥ 7							*A meta-analysis was used to combine the results of the TRANSFORM-1, TRANSFORM-2 and TRANSFORM-3 studies. For the MSM ≥ 7 and MSM ≥ 8 subpopulation the meta-analyses was conducted using fixed effects model whereas a random effects model was used for the MSM ≥ 9 subpopulation. The metric is, mean difference.*
		MSM ≥ 8							
		MSM ≥ 9							

8.3 Forest plots for clinical question 1

8.3.1 SAE – TRANSFORM-1, 2 and 3

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

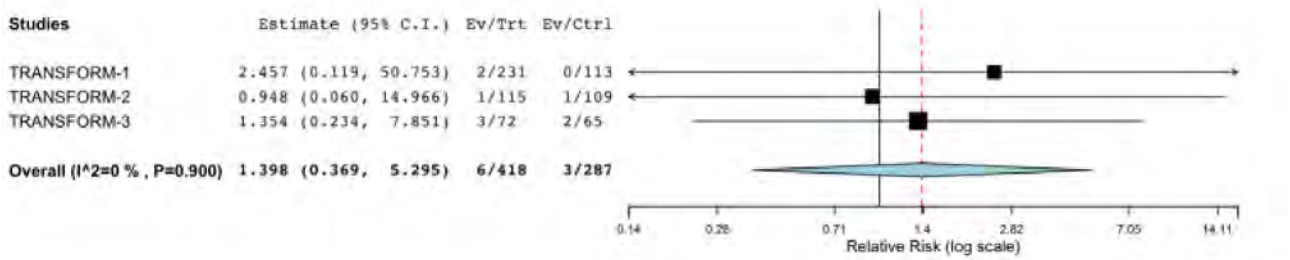
Estimate	Lower bound	Upper bound	p-Value
1.398	0.369	5.295	0.622

Heterogeneity

Q(df=2)	Het. p-Value
0.211	0.900

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.335	-0.966	1.667	0.679



8.3.2 Discontinuation - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

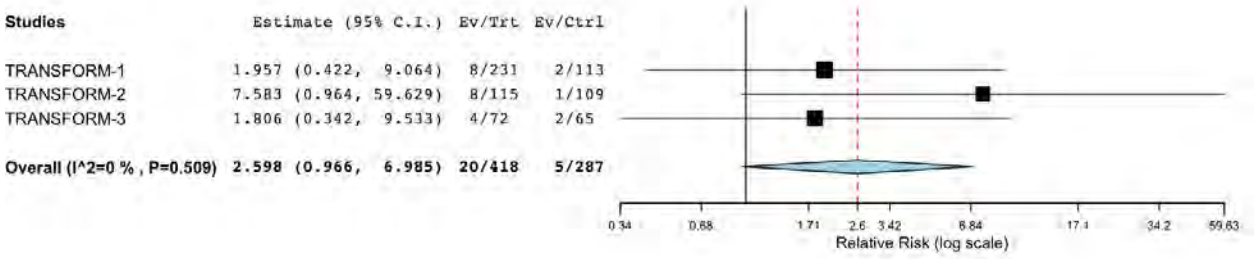
Estimate	Lower bound	Upper bound	p-Value
2.598	0.966	6.985	0.059

Heterogeneity

Q(df=2)	Het. p-Value
1.351	0.509

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.955	-0.035	1.944	0.505



8.3.3 Remission - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

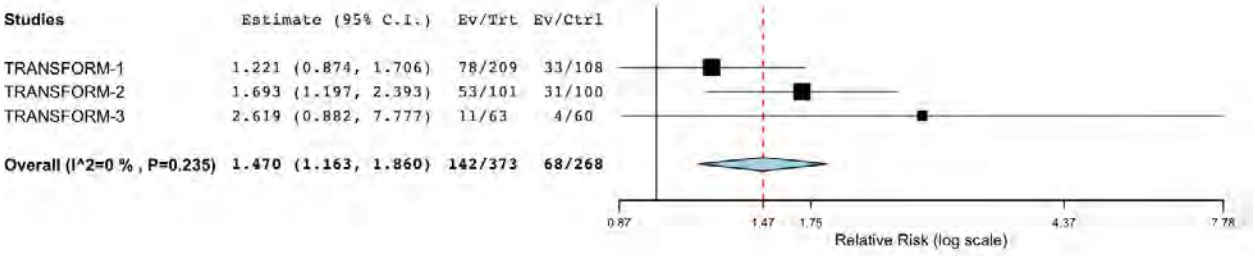
Estimate	Lower bound	Upper bound	p-Value
1.470	1.163	1.860	0.001

Heterogeneity

Q(df=2)	Het. p-Value
2.900	0.235

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.386	0.151	0.620	0.120



8.3.4 Response - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

Model Results

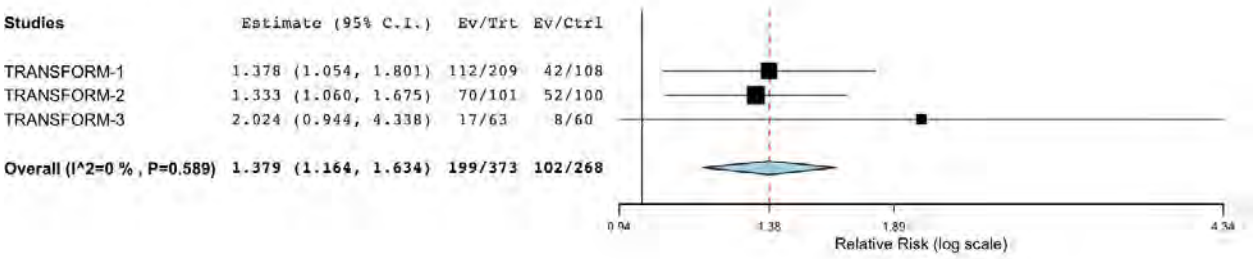
Estimate	Lower bound	Upper bound	p-Value
1.379	1.164	1.634	< 0.001

Heterogeneity

Q(df=2)	Het. p-Value
1.058	0.589

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
0.321	0.152	0.491	0.087



8.3.5 EQ-5D-5L - TRANSFORM-1, 2 and 3

Summary:

Continuous Fixed-Effect Model

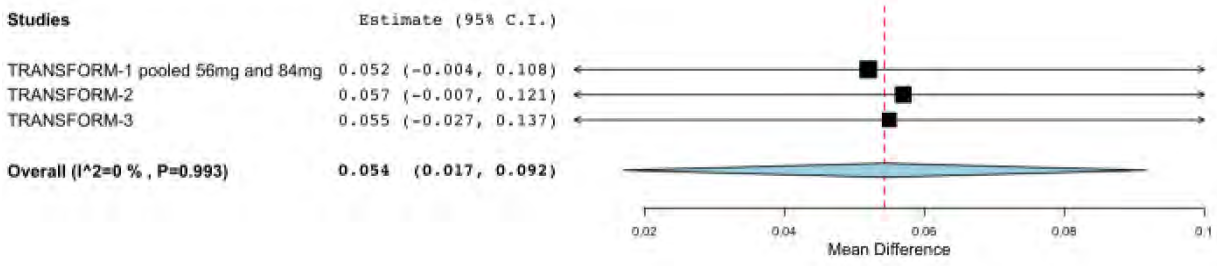
Metric: Mean Difference

Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
0.054	0.017	0.092	0.019	0.004

Heterogeneity

Q(df=3)	Het. p-Value
0.014	0.993



8.4 Forest plots for clinical question 2

8.4.1 Remission for MSM ≥ 7 - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

8.4.2 Remission for MSM ≥ 8 - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

8.4.3 Remission for MSM ≥ 9 - TRANSFORM-1, 2 and 3

Summary:

Binary Random-Effects Model
Metric: Relative Risk

8.4.4 Response for MSM ≥ 7 - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

8.4.5 Response for MSM ≥ 8 - TRANSFORM-1, 2 and 3

Summary:

Binary Fixed-Effect Model - Inverse Variance
Metric: Relative Risk

8.4.6 Response for MSM ≥ 9 - TRANSFORM-1, 2 and 3

Summary:

Binary Random-Effects Model
Metric: Relative Risk

8.4.7 EQ-5D-5L for MSM ≥ 7 - TRANSFORM-1, 2 and 3

Summary:

Fixed-Effect Model

Metric: Mean Difference

8.4.8 EQ-5D-5L for MSM ≥ 8 - TRANSFORM-1, 2 and 3

Summary:

Fixed-Effect Model

Metric: Mean Difference

8.4.9 EQ-5D-5L for MSM ≥ 9 - TRANSFORM-1, 2 and 3

Summary:

Random-Effects Model
Metric: Mean Difference

8.5 ITC of SUSTAIN-2 and the TRD cohort study

8.5.1 Methodology of the ITC

8.5.1.1 Introduction and objectives

Esketamine nasal spray (in combination with an SSRI or SNRI) received marketing authorisation for TRD in the European region in December 2019, making it the first drug approved with a specific indication for TRD in Europe. The esketamine nasal spray clinical development programme in TRD (non-response to ≥2 oral antidepressant treatments in the current episode of depression) consisted of 3 randomised, double blind, short term (4 week) trials; TRANSFORM-1, -2 & -3 and 2 long term trials; a randomised maintenance of effect study SUSTAIN-1 and an open label safety study SUSTAIN-2. In the randomised trials (TRANSFORM-1, -2 & -3 and SUSTAIN-1) esketamine nasal spray + a newly initiated SSRI or SNRI was compared to a newly initiated SSRI or SNRI + placebo nasal spray, meaning esketamine nasal spray + SSRI or SNRI was compared to monotherapy with SSRI or SNRI in the registrational trials. Data indicate monotherapy with an antidepressant is one of the treatments commonly used to treat TRD in Denmark.(89) In many instances the other commonly used strategies are not approved for TRD. For this reason, the most appropriate comparator for esketamine nasal spray, in the context of a registrational clinical development programme and in collaboration with the European Medicines Agency was monotherapy with a newly initiated antidepressant. As such the short- and long-term evidence for efficacy of esketamine nasal spray is versus just one of the possible treatment strategies for TRD and there is a lack of evidence supporting efficacy of esketamine nasal spray versus other treatment strategies.

The European Observational TRD cohort was a non-interventional, prospective cohort study which aimed to collect data from routine clinical practice for TRD (having at least 2 registered failures in the current depressive episode (≤25% improvement on best day, on a treatment taken for at least 6 weeks at adequate dose) prior to baseline. As well as collecting data on the demographics and characteristics of patients with TRD in Europe, the study examined current treatment patterns and treatment outcomes in TRD. As such the study provides important information on the commonly used treatment strategies and clinical outcomes of those strategies in a cohort of European patients with TRD.

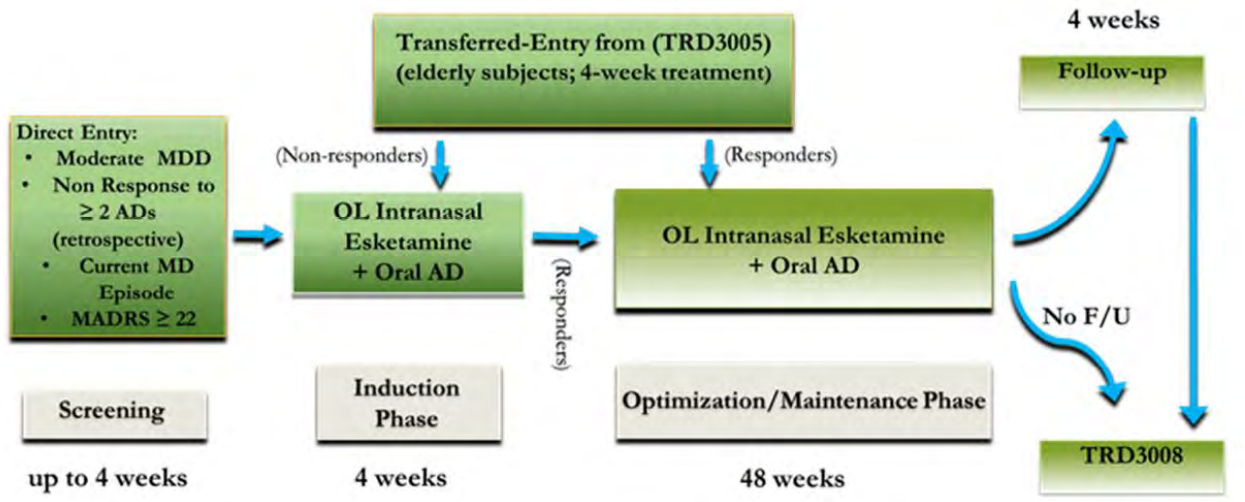
The aim of the current analysis was to generate (indirect) comparative evidence of esketamine nasal spray versus commonly used treatment strategies for TRD, in addition to the evidence generated versus SSRI or SNRI monotherapy for the registrational trials. The European Observational TRD cohort was deemed an appropriate source for clinical outcomes for commonly used TRD treatment strategies, since as described above, it collected data from routine clinical practice for TRD. The long-term, open label study, SUSTAIN-2 was selected as the most appropriate to compare to The European Observational TRD Cohort, since of the esketamine nasal spray trials it best reflects how esketamine nasal spray is expected to be used in clinical (open-label, flexible dosing, 4 week check point for continuing treatment – similar to what is outlined in the esketamine nasal spray label).

8.5.1.2 Overview of SUSTAIN-2 and The European Observational TRD Cohort study Designs

8.5.1.2.1 SUSTAIN 2 and The European observational TRD cohort study designs

SUSTAIN 2 was an open-label, long term, global study that evaluated safety and efficacy of nasal esketamine spray plus a newly initiated oral antidepressant in subjects with TRD (non-response to ≥2 oral antidepressant treatments in the current episode of depression). The study enrolled 802 patients that either entered the study directly (referred to as 'direct-entry subjects') or after completing the double-blind induction phase of the acute TRANSFORM-3 study, a short-term efficacy study in elderly (≥65 years of age) subjects with TRD (referred to as 'transferred-entry subjects'). The study was comprised of 4 phases; a 4-week screening phase (direct-entry subjects only), a 4-week induction phase (direct-entry subjects and transferred-entry non-responder subjects), a 48-week optimization/maintenance phase (all responder subjects from the open-label induction phase of the current study, and transferred-entry responder subjects), and a 4-week follow-up phase (for all subjects). A diagrammatic representation of the study design is provided in Figure 32.

Figure 32: SUSTAIN 2 Study Design



If a subject withdrew from the study before the end of the optimization/maintenance phase for reasons other than withdrawal of consent, they entered the follow-up phase. All direct-entry subjects (who met the entry criteria) started open label nasal esketamine spray treatment as well as a newly initiated oral antidepressant medication on Day 1 of the induction phase. Transferred-entry subjects, who were non-responder in TRANSFORM-3, joined the induction phase. These subjects received nasal esketamine spray and continued the same oral antidepressant treatment that they started in the double-blind induction phase of TRANSFORM-3. Transferred-entry subjects who were responders in TRANSFORM-3, joined the study in the optimization/maintenance phase. These subjects received nasal esketamine spray in an open-label manner and continued the same oral antidepressant treatment (at the same dose) that they were taking at the end of the double-blind induction phase of study TRANSFORM-3. For the present analysis only direct entry subjects were considered.

The end of the study occurred when at least 300 subjects received treatment with intranasal esketamine for 6 months and at least 100 subjects for 12 months. When this was reached, all patients still in the study were withdrawn from it, with "study terminated by sponsor" as reason for withdrawal.

The European observational TRD cohort was a prospective, multicentre, European, observational cohort study to document and evaluate the socio-demographic, disease-related and treatment-related characteristics of patients with MDD who fulfilled the most commonly adopted criteria for TRD (at least 2 registered failures (≤25% improvement on best day, on a treatment taken for at least 6 weeks at adequate dose) prior to baseline according to the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ)) and to document outcomes in routine clinical practice across the European region. In the final analysis set, the study contained 411 TRD patients, aged 18 to 74 years, who were initiating or planned to initiate a new antidepressive treatment regimen. In the context of the cohort, initiation of a new antidepressant treatment was any pharmacological and/or non-pharmacological (e.g., ElectroConvulsive Therapy [ECT], Transcranial Magnetic Stimulation [TMS], specific psychotherapy [i.e., cognitive behavioural therapy [CBT], interpersonal therapy [IPT]], etc.) treatment that was prescribed either to replace or was prescribed in addition to (i.e., on top of) the previously established antidepressant treatment with the intent to improve a patient's clinical depressive condition. Since this was a non-interventional study only data within clinical routine practice, through routine therapeutic procedures and diagnostic assessments were recorded. Baseline date corresponded to the day of the first intake/application of a new antidepressive treatment. After baseline data collection, patients were followed through an observational period of at least 6 months and up to 21 months during which data collection was event-driven, triggered by any clinically relevant worsening or improvement in the current depressive episode. It was also instructed for data to be collected at approximately 6, 12 and 18 months after baseline and/or at the end of the observation period.

8.5.1.2.2 Differences in design

Due to the different types of studies (open-label, clinical trial versus non-interventional, prospective cohort), there are some key differences for consideration in the two studies being compared, as outlined below.

8.5.1.2.3 Schedule of Assessments

In SUSTAIN-2 depression symptoms and severity of depression (using MADRS and CGI-S) were measured at each scheduled visit for each phase of the study (2 times per week during induction and every week during maintenance). The proportion of subjects who responded and remitted, based on MADRS, was calculated over time for each phase. Patient reported outcomes, including EQ-5D-5L and SDS were measured at baseline, day 15 and at day 28 during the double blind induction phase. During the maintenance phase EQ-5D-5L and SDS were measured week 1 and every 2 weeks from week 1 onwards (i.e. week 3, week 5, etc.). The baseline visit for maintenance phase corresponded to the day 28 visit of the induction phase.
The European observational TRD cohort also included the assessment of depression symptoms and severity using MADRS and CGI-S and the patient reported outcomes EQ-5D-5L and SDS. In contrast to SUSTAIN-2, after baseline data collection, patients in The European observational TRD cohort were followed through an observational period of at least 6 months and up to 21 months during which data collection was event-driven, triggered by any clinically relevant worsening, change of treatment or improvement in the current depressive episode. The only pre-specified instructed data collection timepoint was at 6 months and at 12 and 18 months for those patients who reached those timepoints. As such only baseline and 6-month assessments were available for all subjects in The European observational TRD cohort.
Due to the difference in the clinical assessment in the studies, the comparisons (as outlined in section "Comparison") will be based on the 6 month assessment from both studies.

8.5.1.2.4 Study termination

SUSTAIN 2 was terminated when a pre-specified number of patients had received 6 and 12 months of treatment; The end of the study occurred when at least 300 subjects received treatment with esketamine for 6 months and at least 100 subjects for 12 months. As a result of this study design element most subjects did not complete the maintenance phase and a large proportion (54.9%) of subjects stopped the study before completion of the maintenance phase. This group of patients, which represent over half the study population creates an additional source of discontinuations ("study terminated by sponsor"), that does not reflect a treatment effect, but rather a result of the study design. This group of subjects are considered in the analysis by applying partial NRI, (see section "definition of endpoints)

The European observational TRD cohort was stopped when the last enrolled patient reached 6 months of follow-up and there were no withdrawals due to study termination prior to that timepoint.

8.5.1.3 Study populations

8.5.1.3.1 Inclusion/exclusion criteria

The major inclusion/exclusion criteria of SUSTAIN-2 and the European observational TRD cohort were similar, which allows for indirect comparison. Both studies recruited subjects

- ≥18 years of age (up to 74 years for EUROPEAN OBSERVATIONAL TRD COHORT, no upper age limit for SUSTAIN 2)
- who had a diagnosis of MDD without psychotic features
- who met the criteria for treatment resistant depression (TRD) defined as having at least 2 registered failures to respond to antidepressant treatment in the current MDD episode (≤25% improvement of depressive symptoms) according to the MGH-ATRQ
- with a total MADRS score at baseline of ≥22 in SUSTAIN 2 or ≥20 in the European observational TRD cohort

8.5.1.3.2 Baseline Characteristics

The major baseline characteristics of SUSTAIN 2 and the European observational TRD cohort were similar. The main baseline characteristics of both studies are outlined in Table A5.

Table A5: Major baseline characteristics of patients enrolled in SUSTAIN 2 and the European observational TRD cohort

	SUSTAIN-2	TRD cohort
Characteristics	**ESK + AD (SNRI/SSRI)**	**SOC**
N Patients	**N=689[a]**	**N=335[b]**
Demographic characteristics		
Age		
N	689	335
< 30	53 (7.7%)	18 (5.4%)
30-44	171 (24.8%)	58 (17.3%)
45-64	398 (57.8%)	241 (71.9%)
>=65	67 (9.7%)	18 (5.4%)

	SUSTAIN-2	TRD cohort
Characteristics	**ESK + AD (SNRI/SSRI)**	**SOC**
N Patients	**N=689[a]**	**N=335[b]**
Gender		
N	689	335
Male	252 (36.6%)	125 (37.3%)
Female	437 (63.4%)	210 (62.7%)
Disease-related characteristics		
Age at MDD diagnosis		
N	689	335
<35	350 (50.8%)	139 (41.5%)
35-54	290 (42.1%)	166 (49.6%)
>=55	49 (7.1%)	30 (9.0%)
Time since diagnosis		
N	689	335
<5 years	142 (20.6%)	91 (27.2%)
5-19 years	353 (51.2%)	145 (43.3%)
>= 20 years	194 (28.2%)	99 (29.5%)
Total MADRS score		
N	689	335
< 31	338 (49.1%)	146 (43.6%)
31-34	188 (27.3%)	74 (22.1%)
> 34	163 (23.7%)	115 (34.3%)
CGI-S total score at baseline		
N	689	266
1-4	208 (30.2%)	89 (33.5%)
5	361 (52.4%)	136 (51.1%)
6-7	120 (17.4%)	41 (15.4%)
Screening C-SSRSs (lifetime)		
N	689	279
No suicidal thoughts or suicidal behaviour	413 (59.9%)	145 (51.9%)
Suicidal thoughts	168 (24.4%)	104 (37.3%)
Suicidal behaviour	108 (15.7%)	30 (10.8%)
EQ-VAS total score at baseline		
N	689	263
<30	164 (23.8%)	67 (25.5%)

	SUSTAIN-2	TRD cohort
Characteristics	**ESK + AD (SNRI/SSRI)**	**SOC**
N Patients	**N=689[a]**	**N=335[b]**
>=30	525 (76.2%)	196 (74.5%)
Duration of the current episode (weeks)		
N	689	335
<=32 weeks	202 (29.3%)	55 (16.4%)
33-51 weeks	89 (12.9%)	55 (16.4%)
52-103 weeks	135 (19.6%)	88 (26.3%)
>=104 weeks	263 (38.2%)	137 (40.9%)
Number of prior treatment failures		
N	689	335
2nd	409 (59.4%)	179 (53.4%)
3	163 (23.7%)	107 (31.9%)
>=4	117 (17.0%)	49 (14.6%)
Number of episodes		
N	688	329
1	97 (14.1%)	75 (22.8%)
2-5	464 (67.4%)	189 (57.4%)
<5	127 (18.5%)	65 (19.8%)
Average treatment duration in one episode		
N	689	335
<12	183 (26.6%)	8 (11.3%)
12-23	164 (23.8%)	118 (35.2%)
24-51	160 (23.2%)	88 (26.3%)
>=52	182 (26.4%)	91 (27.2%)
Prior failure with augmentation therapy		
N	689	335
No	567 (82.3%)	292 (87.2%)
Yes	122 (17.7%)	43 (12.8%)
Previous failure with SSRIs		
N	689	335
No	168 (24.4%)	63 (18.8%)
Yes	521 (75.6%)	272 (81.2%)
Previous failure with SNRIs		
N	689	335

	SUSTAIN-2	TRD cohort
Characteristics	**ESK + AD (SNRI/SSRI)**	**SOC**
N Patients	**N=689[a]**	**N=335[b]**
No	338 (49.1%)	144 (43.0%)
Yes	351 (50.9%)	191 (57.0%)
Previous failure with TCA		
N	689	335
No	633 (91.9%)	277 (82.7%)
Yes	56 (8.1%)	58 (17.3%)
Previous failure with other therapies		
N	689	335
No	321 (46.6%)	166 (49.6%)
Yes	368 (53.4%)	169 (50.4%)

a: SUSTAIN-2 direct entry patients. Two patients from the SUSTAIN-2 study with only one prior treatment failure were not included in the historical comparison

b: Patients in the TRD cohort who received at least one oral antidepressant therapy at baseline

AD: Antidepressant, CGI-S: Clinical Global Impression of Severity, cm: Centimetre, C-SSRS: Columbia-Suicide Severity Rating Scale, ESK: Esketamine, ITT: Intention to Treat, MADRS: Montgomery-Åsberg Depression Rating Scale, MDD: Major Depression, M: Mean, N: Number of subjects in the ITT-Population, PCB: Placebo, SD: Standard Deviation, SNRIs: Serotonin Noradrenalin Reuptake Inhibitors, SSRIs: Selective Serotonin Re-uptake Inhibitors, TRD: Treatment-resistant Major Depression

8.5.1.4 Comparisons

The main comparison conducted was between patients starting esketamine nasal spray + oral AD (from SUSTAIN-2) versus patients starting an antidepressive treatment involving at least one oral AD from TRD cohort study.

NB: for all comparisons, patients from the TRD cohort study receiving only biological treatments or psychosocial interventions were excluded.

8.5.1.5 Outcomes and endpoints

8.5.1.5.1 Clinician-rated outcomes

The following clinician-rated outcomes will be analysed:

- **Based on MADRS:**
  - **MADRS total score (continuous): change from baseline to month 6**
  - **Clinical response (binary): improvement in MADRS total score of 50% at month 6 or more compared to baseline**
  - **Clinical remission (binary): MADRS total score of 10 or below at month 6**

8.5.1.5.2 Safety outcomes

Adverse Events that occurred during the follow-up of patients in the European observational TRD cohort study were reported via regular pharmaco-vigilance and were not documented within the study itself. As such, no safety data were reported in the European observational TRD cohort, making the indirect comparison between SUSTAIN 2 and the European observational TRD cohort on these outcomes impossible.

8.5.1.6 Definition of endpoints

For SUSTAIN-2, data from week 26 were considered month 6 data. For the European Observational TRD cohort, simple visual data exploration suggested that day 150-216 was an acceptable post-baseline window to consider month 6 data. A similar framework for data handling was used for all types of endpoints:
1) If patients had a month 6 evaluation and were still under initial treatment, their observed value for the evaluation was used in the analyses (e.g. if those patients were in remission at that month 6, they were considered to be in remission)
2) If patients stopped or changed their treatment before month 6, they were considered as experiencing treatment failure (e.g. a patient in remission at month 6, but on another treatment than at the baseline-initiated treatment, was considered a failure). In addition, for the patients in SUSTAIN-2 that were dropping out before month 6 due to study termination were excluded from the analyses (non-informative drop-out).
3) For the patients in the TRD observational cohort study, patients who did not have a registered visit in the month 6 time window (day 150-216), but with a recorded visit after the month 6 window (thus, a visit after day 216 post-baseline), these patients were also considered for the analysis and the same criteria as in point 1) and 2) were applied. In other words, for patients with a post-6 month visit that were still on their initial treatment, their observed value for the evaluation was used in the analysis. Yet, patients with a post-6 month visit that stopped or changed treatment, or left the study, before this visit, were considered a treatment failure.
By following this approach, we were not too conservative when considering treatment response in the standard of care arm from the TRD observation cohort study.

8.5.1.6.1 Binary endpoints

Binary endpoints analysed were response rates at month 6 (MADRS improvement of at least 50% relative to study baseline), remission rates at month 6 (MADRS ≤10).
For those binary endpoints, a non-responder imputation (NRI) was applied in cases which were potentially suggestive of treatment failure. With application of NRI, patients were assumed to have a negative outcome at month 6 (i.e. no response, no remission, no functional remission).
In the SUSTAIN 2, a partial NRI was implemented, and patients who dropped-out from the study before month 6 because of “study terminated by sponsor” (non-informative drop-out, only related to study execution) were excluded from the analysis instead of having their outcome imputed by NRI.
In the TRD observational cohort study, NRI was implemented 1) for patients that dropped out of the study before reaching the month 6 timepoint, as well as 2) for patients who, between baseline and month 6, changed their treatment strategy in a way which could be suggestive for a treatment failure. Specifically, treatment stop (stopping an antidepressant and not initiating a new one), treatment switch (stopping an antidepressant A and starting an antidepressant B), treatment combination (adding antidepressant B on top of antidepressant A) and treatment augmentation (adding augmentation substance X on top of antidepressant A) were considered cases of treatment failure and led to implementation of NRI. Of note, combination stop and an augmentation stop were not considered suggestive of treatment failure and did

not lead to NRI. For the TRD observational study, no distinction was made between full and partial NRI since no discontinuation for study termination occurred before month 6 (i.e. the study was terminated 6 months after the last patient enrolled into the study).
NB: for both studies, the use of an approach like NRI, which is by nature very conservative, leads to response/remission rates that are much lower than those previously reported, due to the imputation.

8.5.1.6.2 Survival endpoints

Binary endpoints could also potentially be analysed as "time to" outcomes using survival analyses methods. However, this was assessed as giving bias in favour of esketamine nasal spray to esketamine due to the large number of interim visits between baseline and month 6 in study SUSTAIN 2 (would give higher chances for patients to reach the outcome – e.g. response – at least once during one of these interim visits).
Therefore, no survival analyses were conducted on the binary endpoints, and these were analysed only as described in previous section.

8.5.1.6.3 Continuous endpoints

Continuous endpoints analysed were MADRS change relative to baseline.
For the continuous endpoint, negative outcome imputation was applied in the form of Baseline Observation Carried Forward (BOCF) approach. With this approach, patients who were identified as having experienced treatment failure (e.g. due to study withdrawal, treatment switch etc.) were assumed to return to their baseline value on the scale (i.e. no change relative to baseline). With this approach, for instance, a patient who switched treatment in the TRD observational cohort study before month 6, had set its MADRS change to baseline equal to zero (i.e. no improvement after baseline).
A partial BOCF was applied in the main analysis (patients who dropped out because of study termination considered missing).

8.5.1.7 Method for indirect comparisons

8.5.1.7.1 Patients included in analyses

Two patients in study SUSTAIN 2 were excluded from the analyses as they had only one previous treatment failure recorded in the MGH-ATRQ (and therefore, had no counterpart in the observational European TRD cohort).
In the TRD observational cohort study, only patients receiving at least 1 oral antidepressive treatment at baseline were included, i.e. patients only receiving a psychosocial treatment (e.g. interpersonal therapy, cognitive behavioral therapy) and/or a biological treatment (e.g. electroconvulsive therapy, transcranial magnetic stimulation) were excluded from the analyses.

8.5.1.7.2 Unadjusted (naïve) comparison

For the unadjusted comparison of binary outcomes, the treatment effect was estimated as an odds ratio with a simple logistic regression model. From the model, the predicted proportions of patients in response and (functional) remission in both arms were also computed.

For the unadjusted comparison of continuous outcomes, the treatment effect was estimated as the mean difference between both treatment arms in terms of change from baseline of the scale at month 6. This was done with a simple linear regression model. From the model, the predicted changes from baseline of the outcomes of both arms were also computed.

8.5.1.7.3 Covariate adjustment approach

For the adjusted comparisons, additional covariates corresponding to patient characteristics were added to the models (logistic regression for binary outcomes, simple linear regression for continuous outcomes) to control for potential imbalances in the distributions of those covariates across the two studies (and therefore, the two treatments involved in the comparison). Covariates were entered sequentially/cumulatively into the model containing treatment effect as the first covariate. By adding the covariates in such sequential/cumulative way, the next covariate was added on top of the other covariates already included. With the approach, adding the last covariate is equivalent to having all covariates simultaneously into the same model. With those additional covariates added into the model, the models produced predicted means, odds ratios and mean differences of the which were adjusted for potential confounding factors. We also took an alternative approach where the variables corresponding to the patient characteristics were selected in the model in a data-driven way using variable selection algorithms. Specifically, the forward, backward, and stepwise variable selection methods were applied with threshold p-values for inclusion and exclusion set to 0.15.

8.5.1.7.4 Weighted comparisons using propensity scores

A commonly cited concern of the classic covariate adjustment approach mentioned in the previous section is that such models might be overfitted when the number of covariates is large compared with the number of patients or outcome events (Chen et al., 2016). To overcome this potential problem, propensity score (PS) methods are used. These methods start with the estimation of a PS for each individual patient. The PS for an individual is defined as the probability of being assigned to the "treatment arm" (as opposed to being assigned to the control arm) given relevant covariates corresponding to the patient characteristics (Austin and Stuart, 2015). The PS is usually estimated using a logistic regression model which incorporates patient covariates that may be related to the outcome and/or the treatment decision. Two sets of approaches have been taken regarding the included patient covariates in the propensity score model. With the first approach, all patient covariates were added sequentially to the model in a cumulative way. With this approach, all patient covariates are included in the model when the last covariate is entered into the model. With the second set of approaches, variable selection was applied such that the model automatically only includes those patient covariates which are predictive of the propensity score (i.e. the probability to be assigned to the treatment arm). Specifically, forward, backward and stepwise variable selection was applied with the threshold p-values for inclusion or exclusion of variables being set to 0.15.

Once the PS have been calculated from the propensity score model, there are several options for how to use them to estimate the adjusted "treatment" effect (Austin and Stuart, 2015). Note throughout that, although PS methods strive to estimate the true "treatment effect," the usual caveats apply, such as the inability to include all unmeasured patient characteristics which may act as confounders (unmeasured confounders.

Using these PS, an inverse probability weighting (IPW) approach was implemented, which weights each observation based on the observation's estimated PS (Abdia et al., 2017). IPW uses the entire dataset but reweights individuals to increase the weights of certain individuals in a way that additional observations are created for those parts of the target population from which there were few observations. In doing so, a

pseudo-population is created with the objective to obtain a near-perfect covariate balance between treatment groups.
Different IPW methods estimating treatment effects in different (pseudo)populations exist (Li et al., 2018). Each IPW method weights the treated and comparator observations to make them representative of the population of interest. A first weighting method leads to estimation of the average treatment effect (ATE), which corresponds to the mean of the individual causal treatment effects in the entire patient population. The ATE can be thought of as the average effect, at the population level, of moving an entire population from control (here: SoC from the European observational TRD cohort) to treated (here: esketamine + oral AD from SUSTAIN 2). The target population is thus the whole population, both treated and controlled. To obtain this target population, patients with unexpected exposures (e.g. a patient assigned to the treatment group but with a low propensity score (i.e. given the patient covariates, a low probability to be assigned to the treatment group according to the propensity score model) are upweighted most and patients with expected exposures (e.g. given the patient covariates, a high probability to be assigned to the treatment group) are upweighted least. Of interest, the Average Treatment Effect (ATE) is generally the quantity estimated when running a *randomized* study.
For the ATE IPW method, stabilized versions of the weights have been generated which prevents some patient weights being too large in case of particularly large or small PS (Thoemmes and Ong, 2015). Stabilized weights thus have lower variance compared to their un-stabilized counterparts.

8.5.1.7.5 List of variables for adjustment and propensity scores

Variable for adjustment considered in the statistical models for the adjusted comparison is given in table A5.1 beneath.

Table A5.1: Variables for adjustment and propensity scores

Rank	Variables for adjustment	Coding
1	Number of previous failures	2 / 3 / 4 or more
2	Age category	<30 / 30-44 / 45-64 / ≥65
3	MADRS baseline severity	<31 / 31-34 / >34
4	Number of episodes	1 (single episode) / 2-5 / 6-10 / >10
5	Duration of current episode	≤32 weeks / 33-51 weeks / 52-103 weeks / ≥104 weeks
6	Sex	Male / Female
7	Previous failure on augmentation	No / Yes
8	Suicidal behavior history	No event / Suicidal ideation / Suicidal behaviour / Missing
9	Time since first MDD diagnosis	<5 years / 5-19 years / ≥20 years
10	Age when first diagnosed	<35 / 35-54 / ≥55
11	Previous failure on SSRI	No / Yes
12	Previous failure on SNRI	No / Yes
13	Previous failure on TCA	No / Yes
14	Previous failure on other ADs	No / Yes
15	Average line duration	<12 weeks / 12-23 weeks / 24-51 weeks / ≥52 weeks
16	CGI-S baseline severity	1-4 / 5 / 6-7 / Missing
17	EQ-VAS baseline	<30 / ≥30 / Missing

8.5.1.8 Subgroup analyses

Sub-populations from both SUSTAIN 2 and the European observational TRD cohort will be selected and compared with each other based on baseline characteristics of the patients, using the same methods as previously described.
Subgroup analyses were conducted for the following sub-populations:

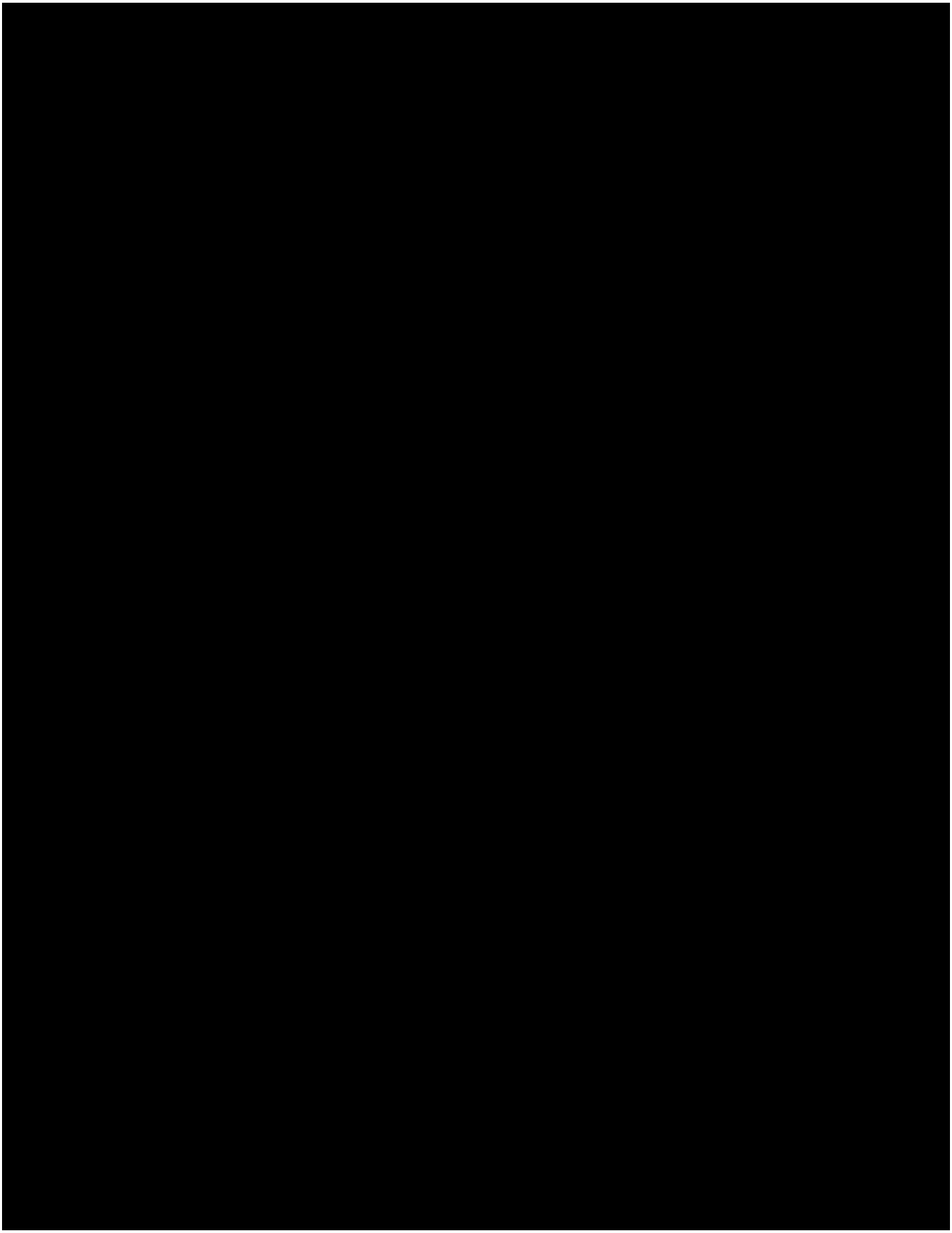
- Patients with a MSM ≥ 7 score
- Patients with a MSM ≥ 8 score
- Patients with a MSM ≥ 9 score

For each of the subpopulations and studies (i.e. TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1 and SUSTAIN-2), the baseline characteristic in terms of the different components of the MSM score are available in table A5.2 to table A5.6. As requested by the Medicines Council as part of the validation process, additional tables presenting baseline characteristics of different MSM groups are available at section 8.5.14.
Generally, the data shows that patients across the three subpopulations are selected to be more "severe" on all criteria (compared to original population), and that the subpopulations have a good diversity of profiles. Furthermore, the MSM ≥ 9 cut-off basically results in selecting the most "severe" patients on all the MSM criteria all at once.

However, there are also a quite similar composition of MSM patient characteristic when comparing the MSM ≥ 8 and MSM ≥ 9 subpopulations. [redacted]

Consequently, as the population size in the MSM ≥ 9 is small (thus increases uncertainties in the results) the results of the MSM ≥ 7 and MSM ≥ 8 groups are relevant in supporting the evaluation of ESK-NS+OAD in terms of efficacy efficacy in more "severe" groups than the full TRD population not having responded on a least two different treatments with antidepressants in the current moderate to severe depressive episode.

[redacted]

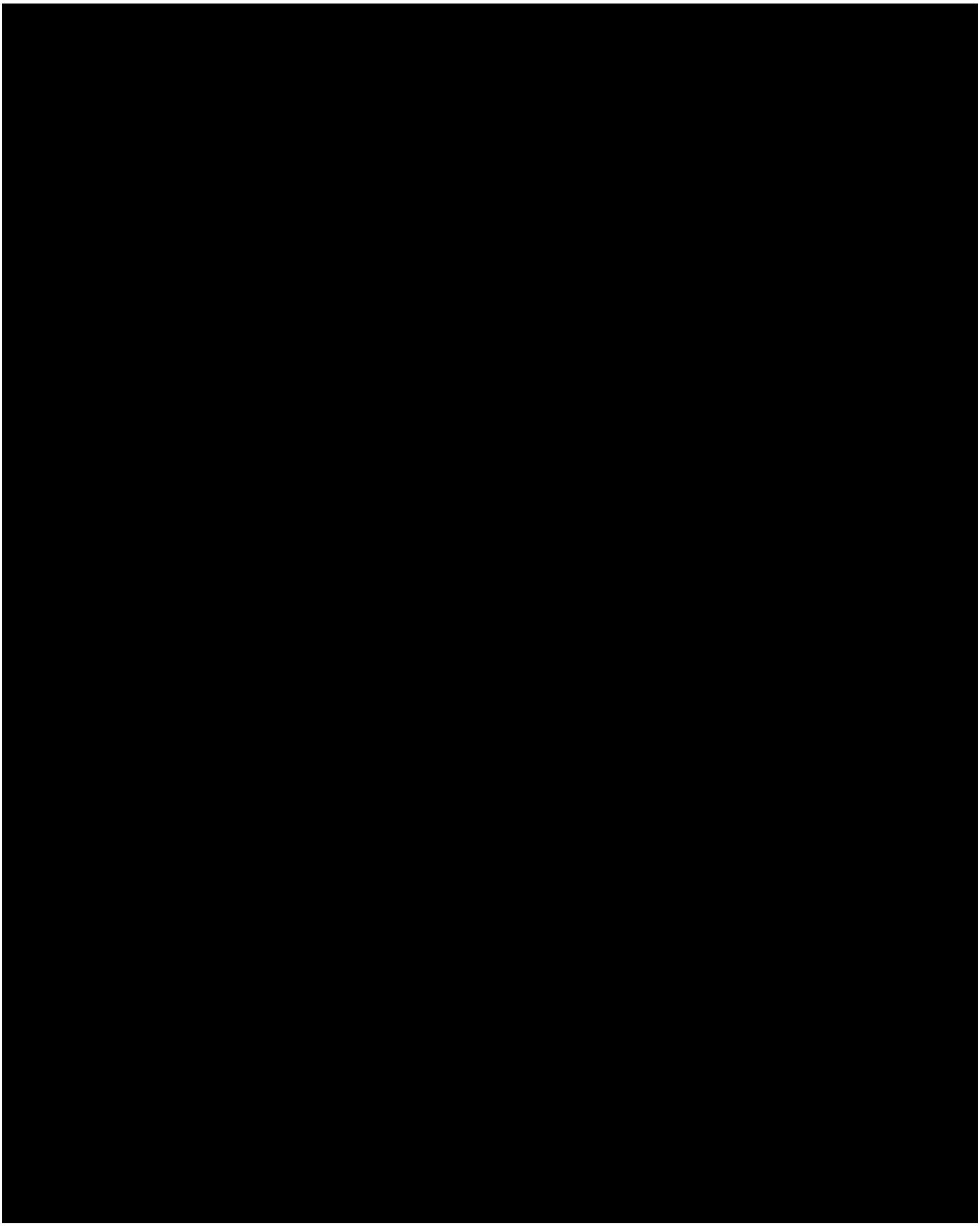


[redacted]

8.5.1.9 Qualitative evaluation of biases

RCT versus real life: patients can be expected to be more compliant and motivated in RCT setting
Frequency of visits is higher in SUSTAIN-2 compared to European observational TRD cohort. Knowing that more frequent contacts with healthcare professionals might lead to improved outcomes for the patients, this could potentially create a bias in favour of esketamine. However, it is worth noting that these frequent contacts between patients and healthcare professionals are expected to reflect the clinical practice for esketamine due to the administration mode of the treatment. As such, these additional visits are not expected to favour esketamine.
In study SUSTAIN-2, only patients achieving response (50% or more improvement on MADRS) at week 4 are allowed to continue treatment beyond this timepoint. Although a similar treatment continuation rule is included in the label of esketamine ("evaluation of therapeutic benefit at week 4"), it can be expected to be less constraining, and to allow more patients to continue treatment beyond week 4 if therapeutic benefit is considered sufficient (even if it does not reach the criterion for response). Given that patients stopping treatment is always considered as a treatment failure, this element of the study design is expected to introduce a bias which disfavours esketamine (and has no effect on the standard of care in European observational TRD cohort study) compared to expected results in clinical practice.
The design of SUSTAIN-2 stipulates that, at study entry, patients initiate esketamine treatment and at the same time a new oral antidepressant. The label of esketamine however includes no recommendation on the initiation of a new antidepressant, and it can be expected that a proportion of patients will start esketamine on top of an already ongoing oral antidepressant. A newly initiated antidepressants could be expected to have better chance of providing therapeutic benefit to the patient, compared to an ongoing one that is not providing sufficient benefit (since patients are treatment resistant). This could create a bias in favour of esketamine compared to its expected results in clinical practice, that will consist in a mix of patients receiving a newly initiated oral AD or an ongoing one.

8.5.2 Remission at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)

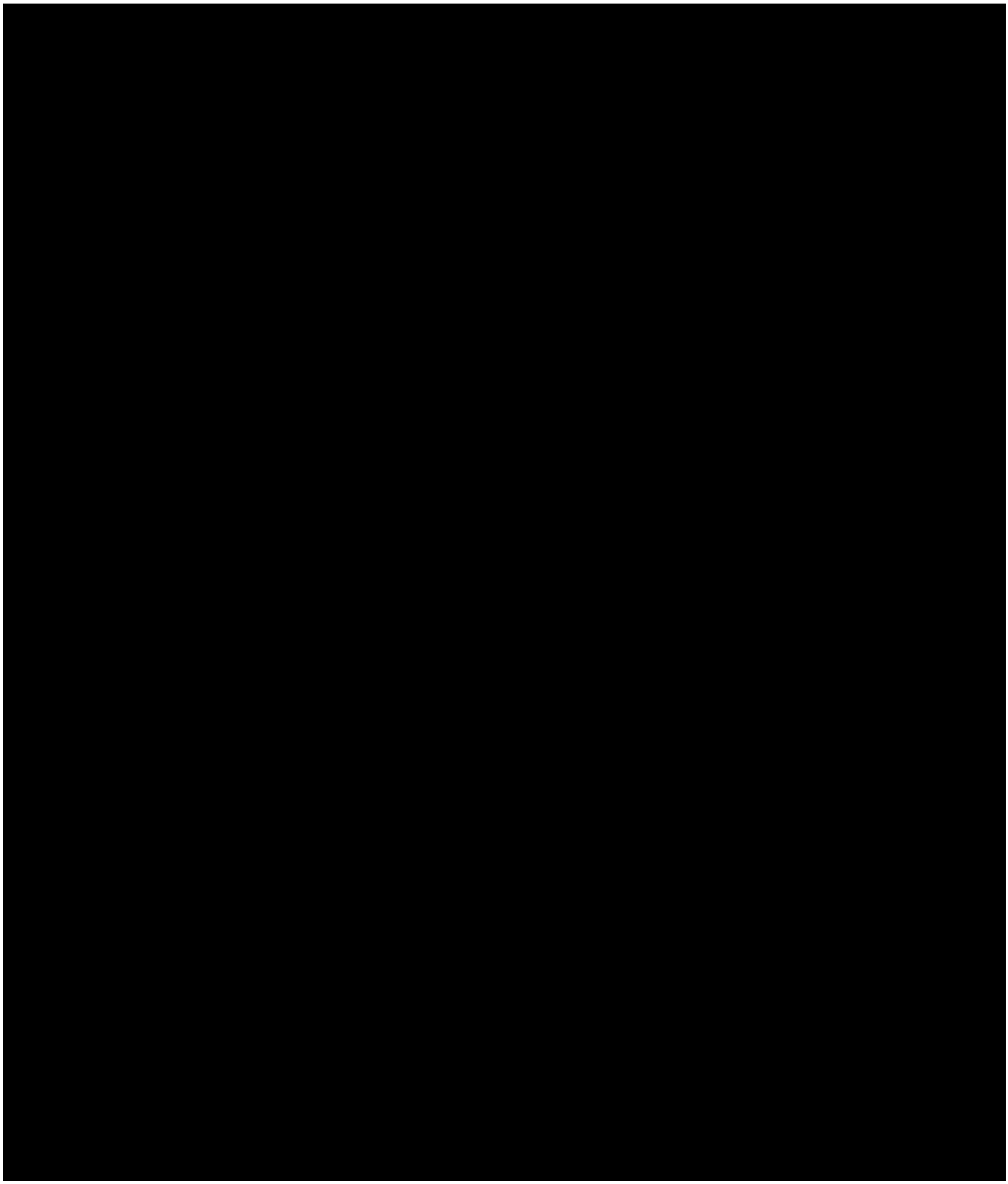


[redacted]

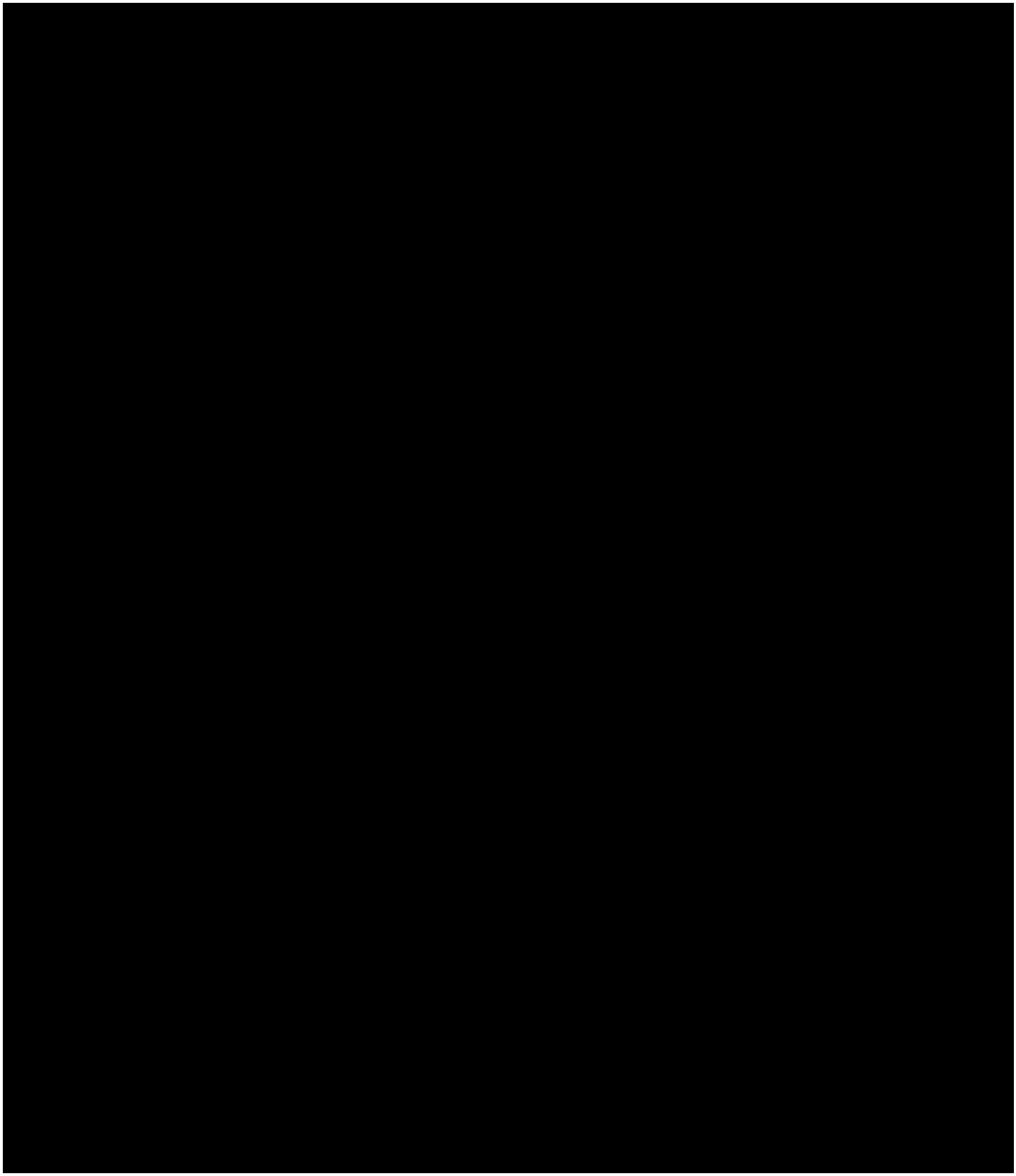
8.5.3 Response at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)

[redacted]

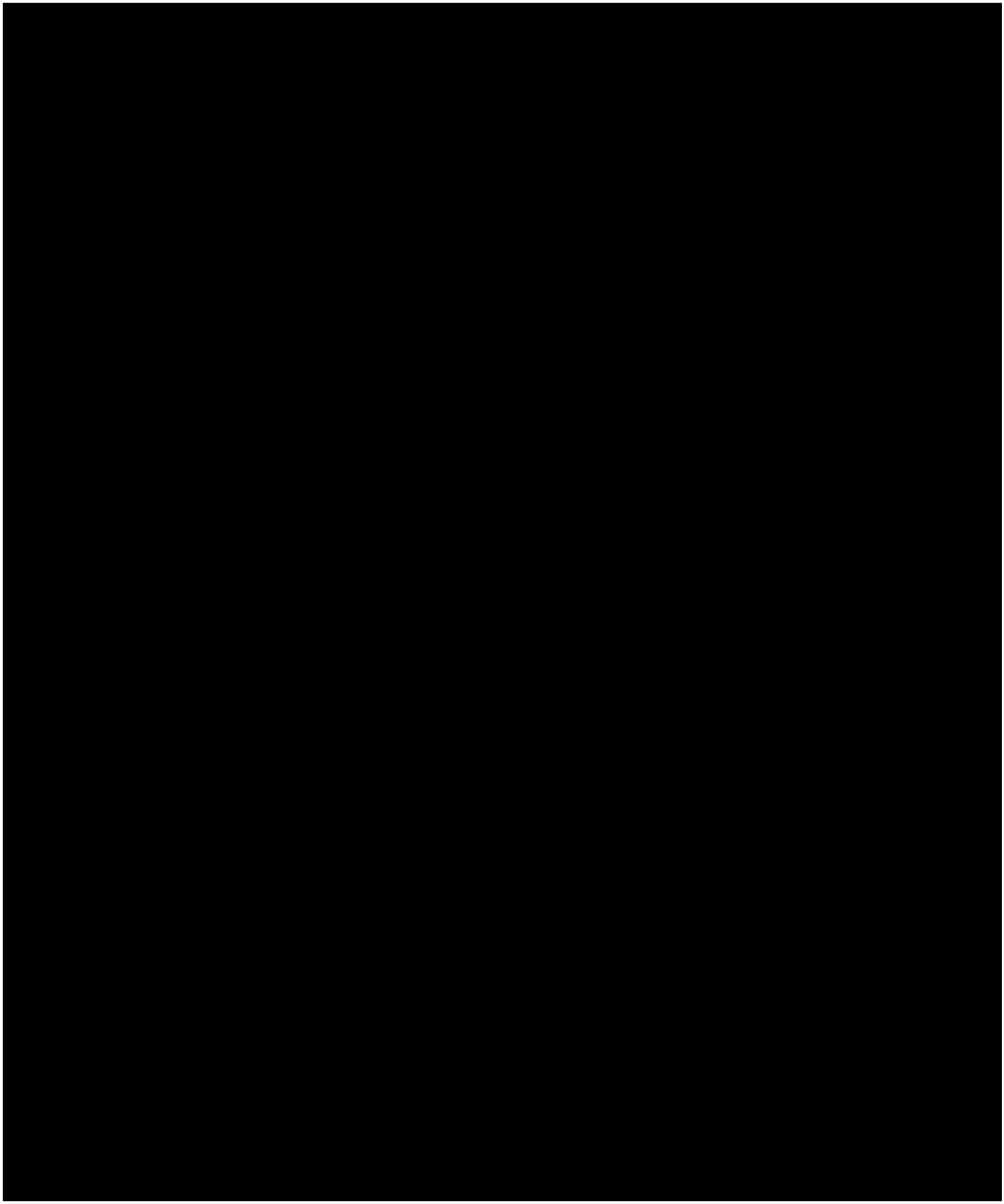
8.5.4 Remission at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 7 population (clinical question 2)



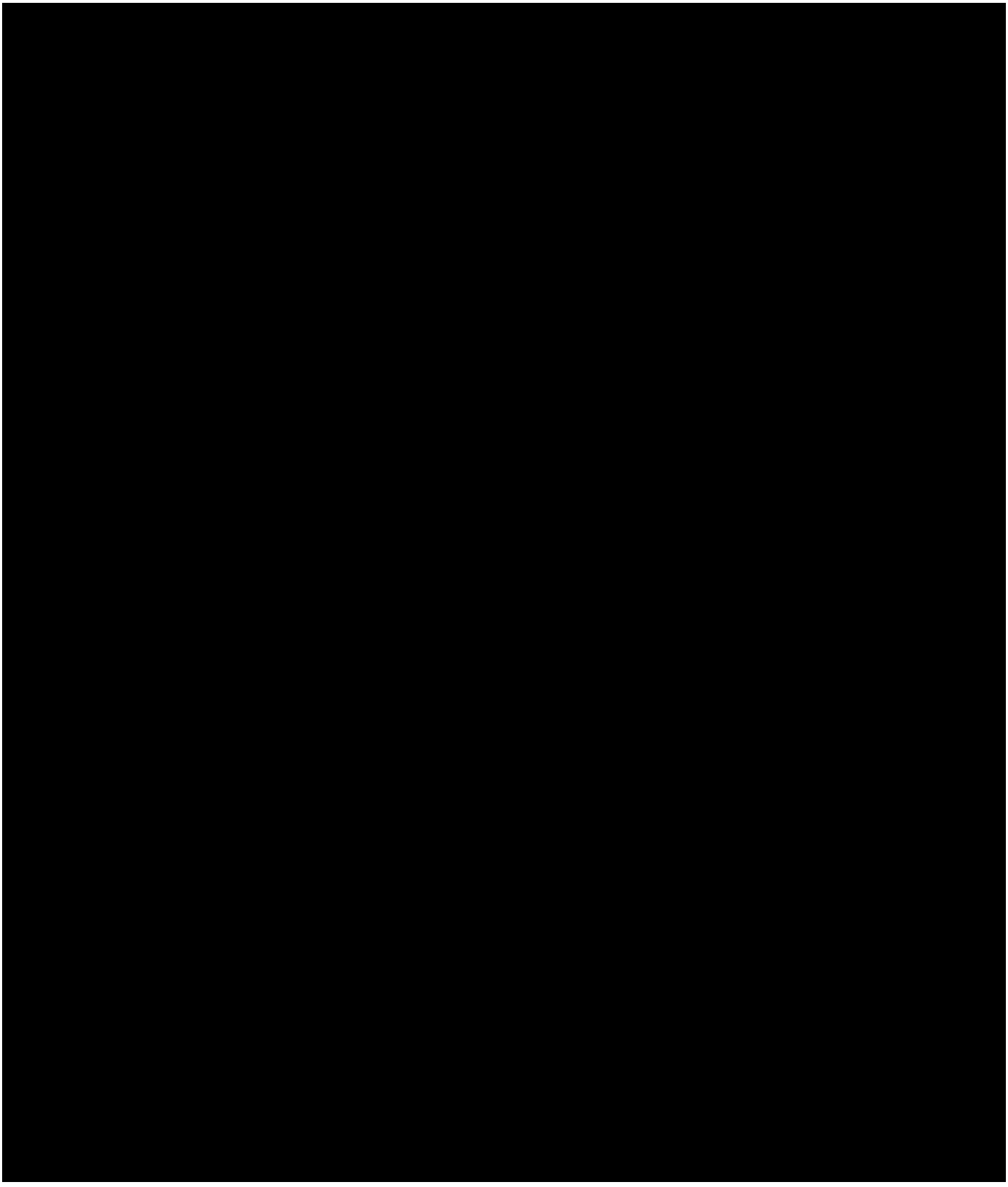
8.5.5 Response at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 7 population (clinical question 2)



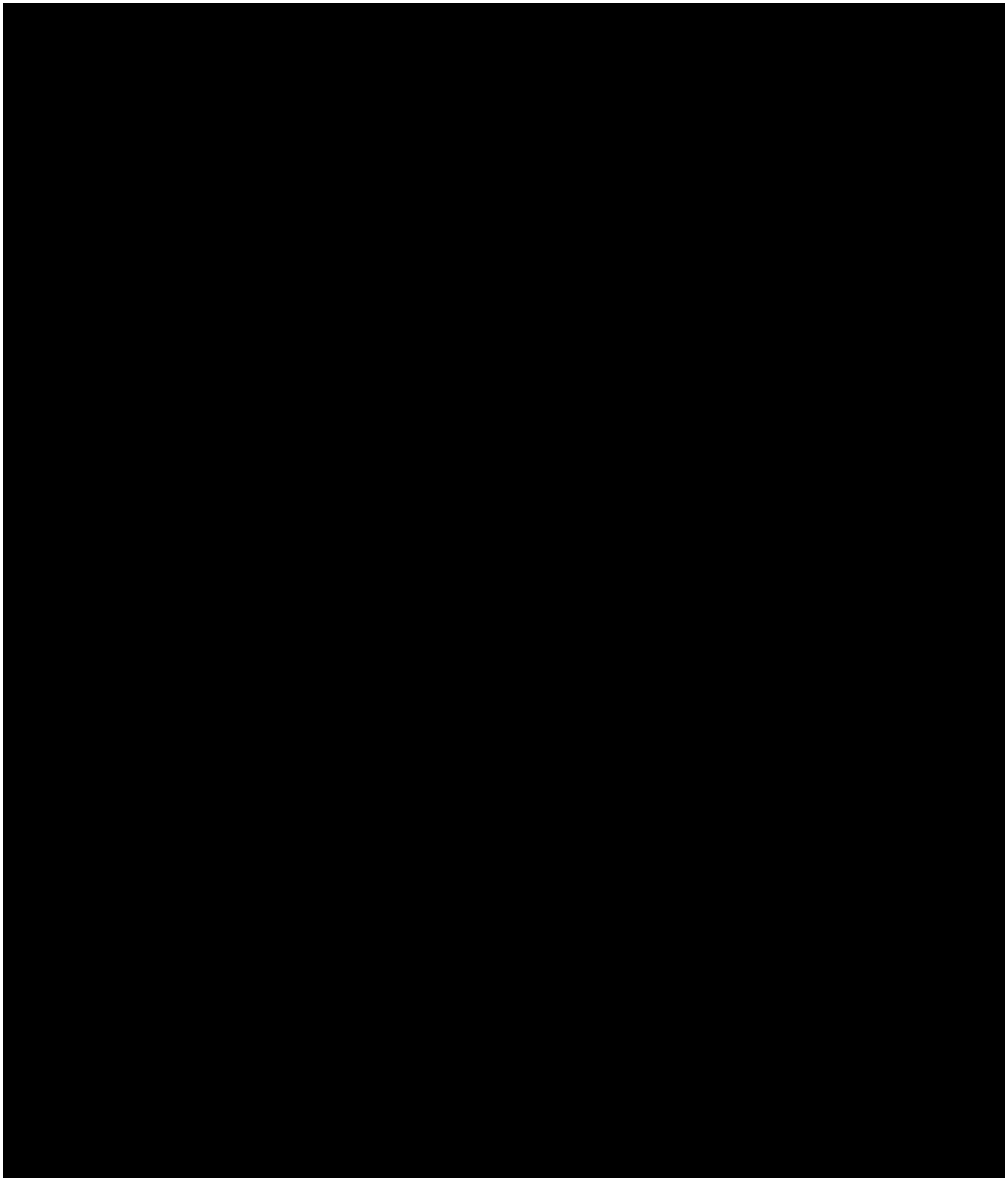
8.5.6 Remission at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 8 population (clinical question 2)



8.5.7 Response at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 8 population (clinical question 2)

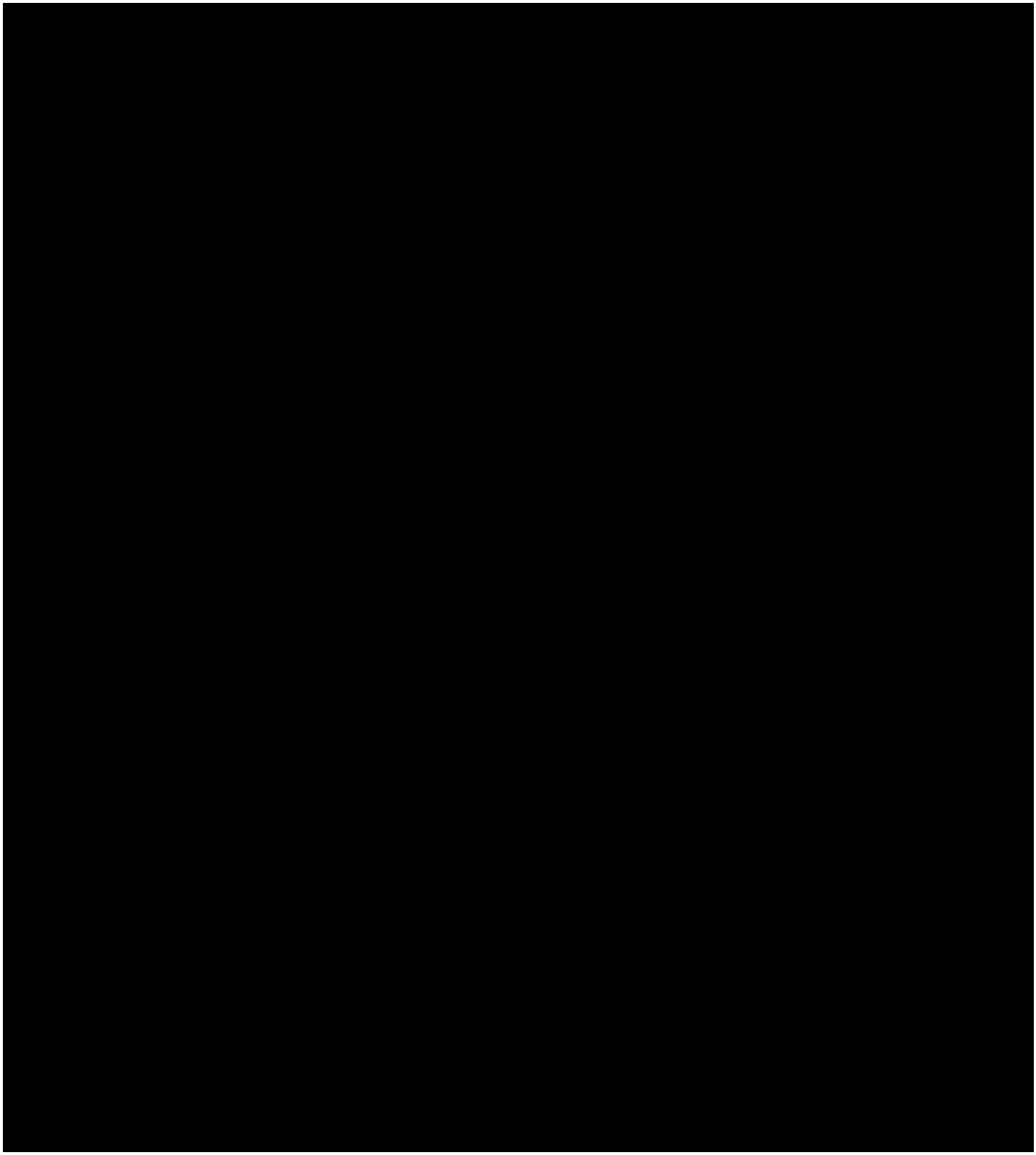


8.5.8 Remission at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 9 population (clinical question 2)

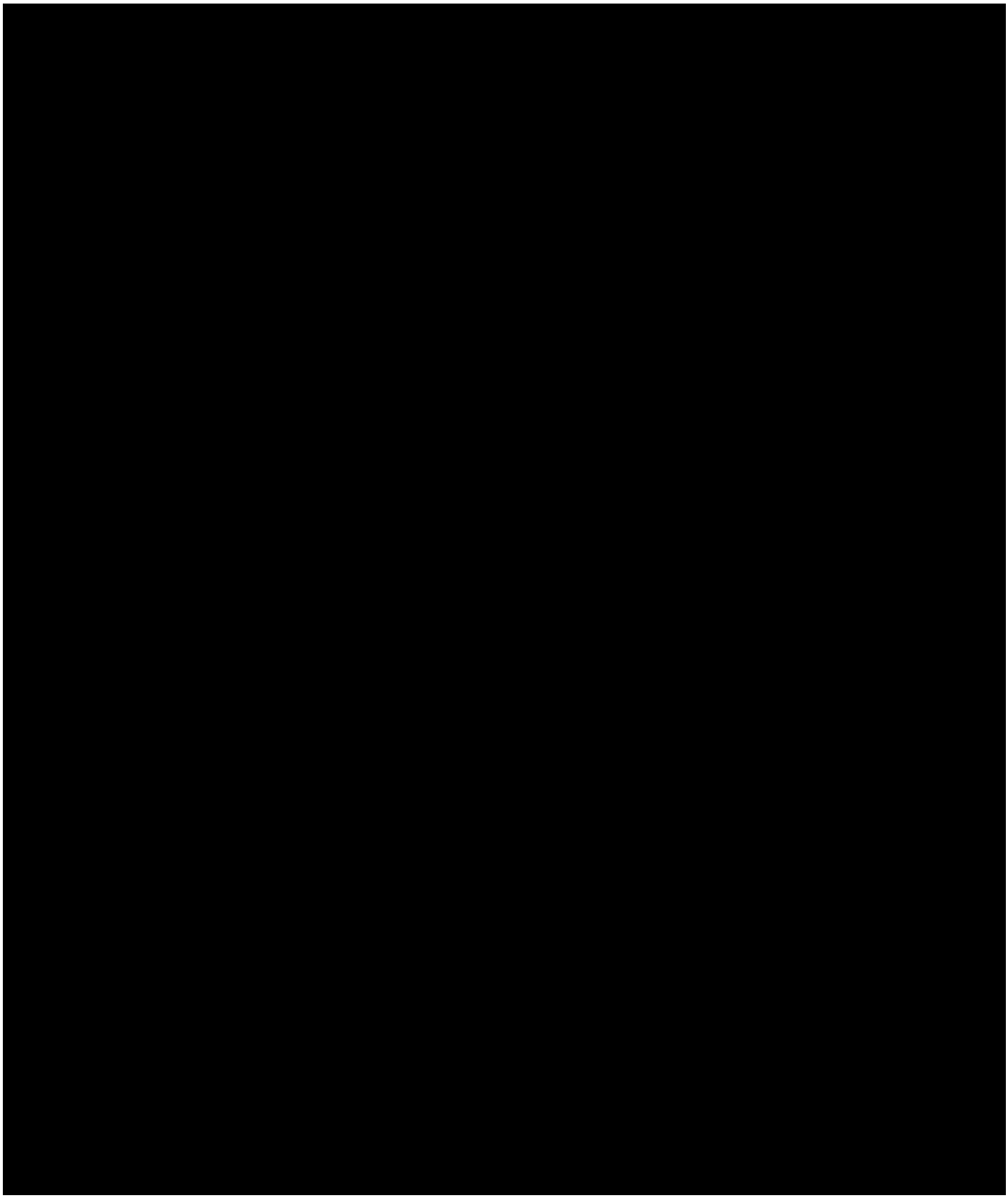


8.5.9 Response at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 9 population (clinical question 2)

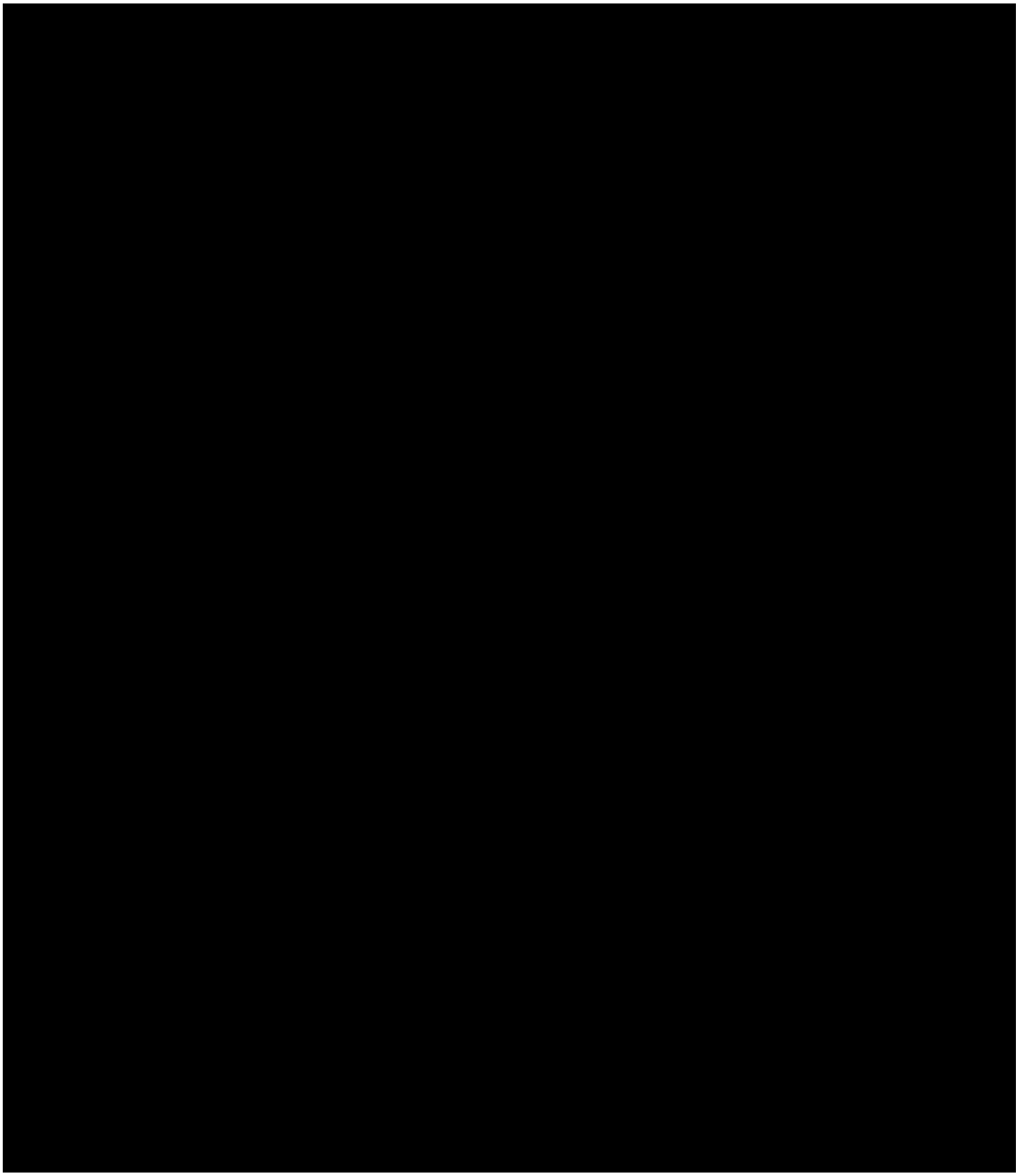
Response at 6 months for the MSM ≥ 9 subpopulation – ITC of SUSTAIN-2 and the TRD cohort study.



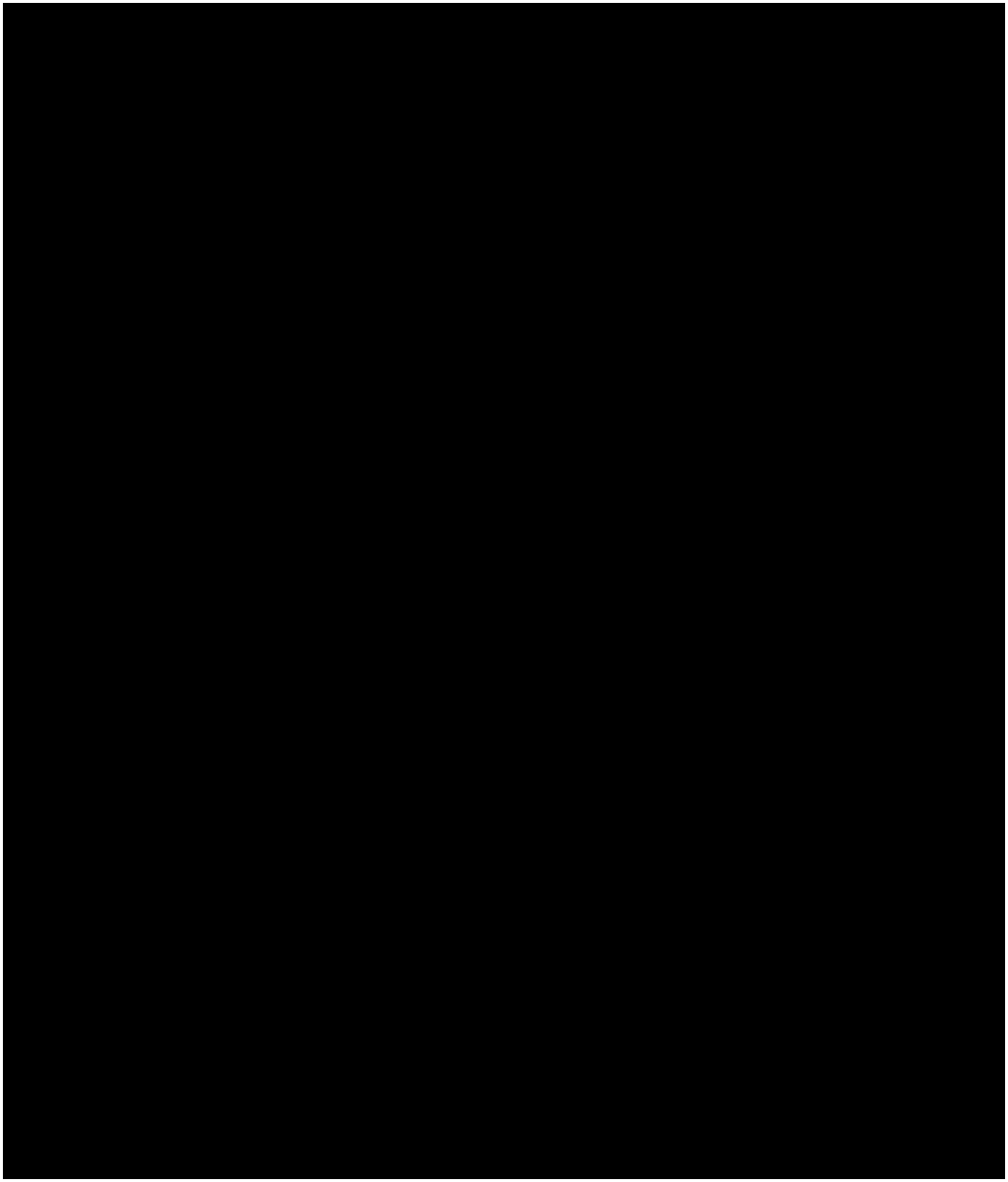
8.5.10 MADRS total score at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)



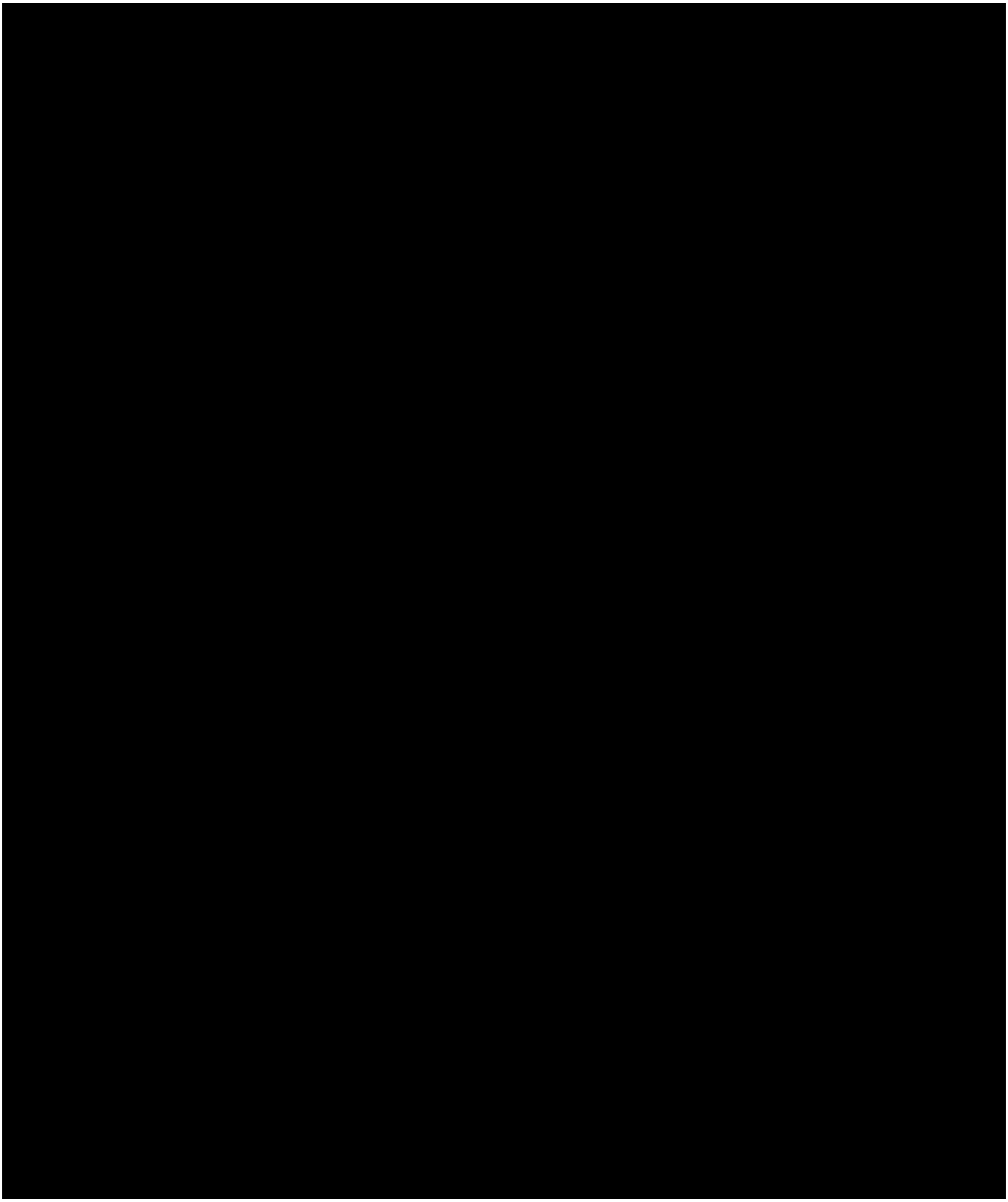
8.5.11 MADRS total score at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 7 population (clinical question 2)



8.5.12 MADRS total score at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 8 population (clinical question 2)



8.5.13 MADRS total score at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 9 population (clinical question 2)



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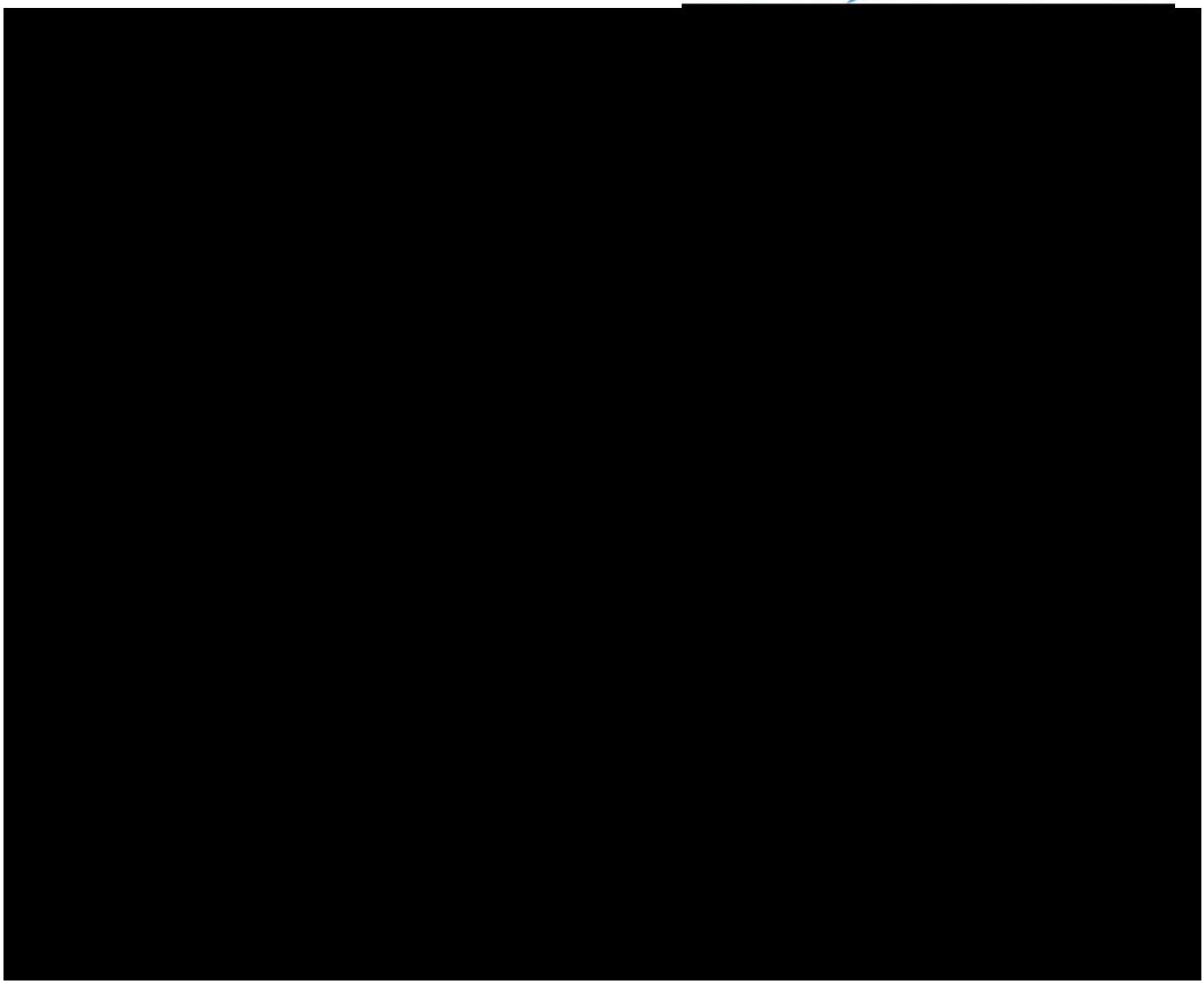
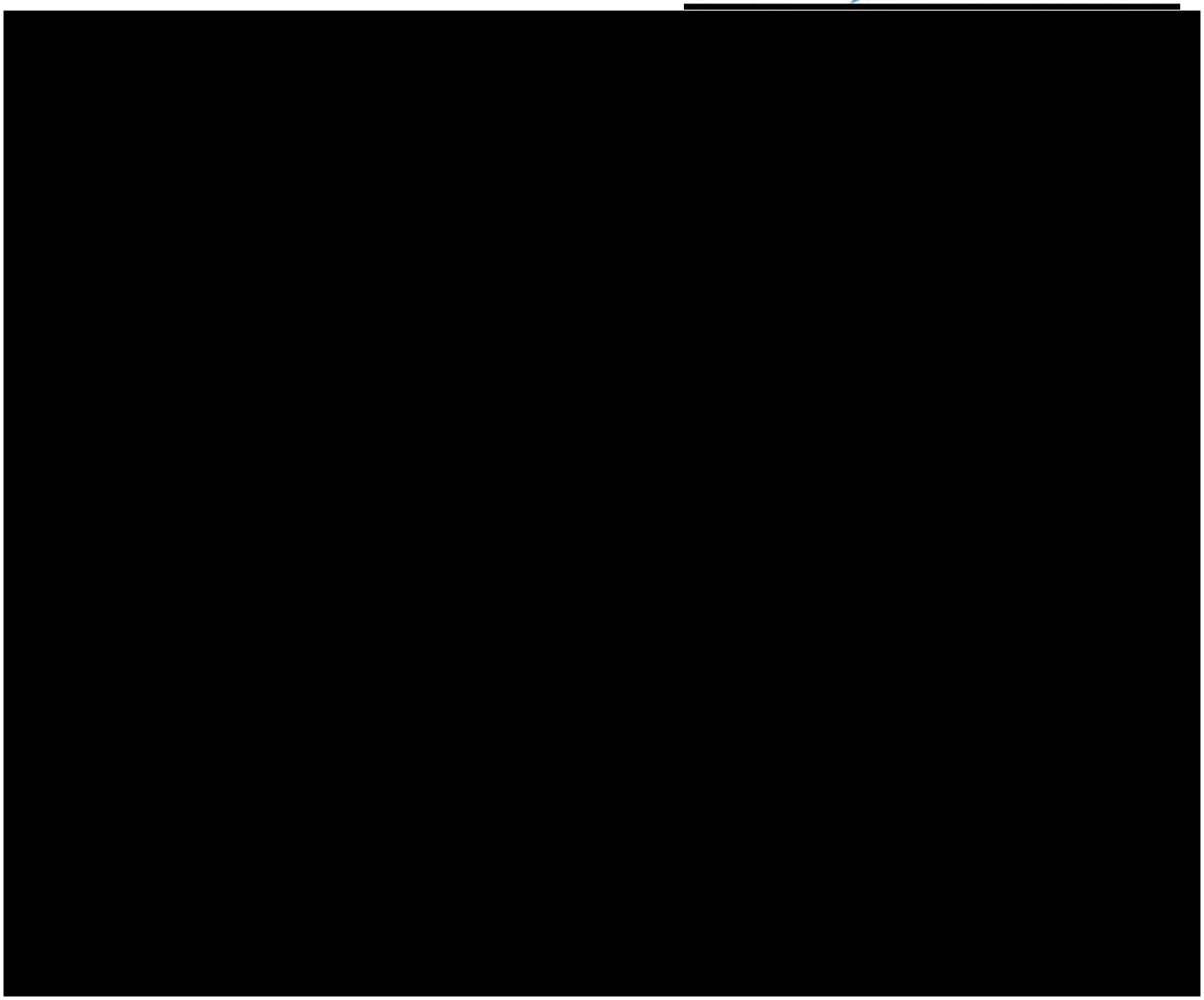
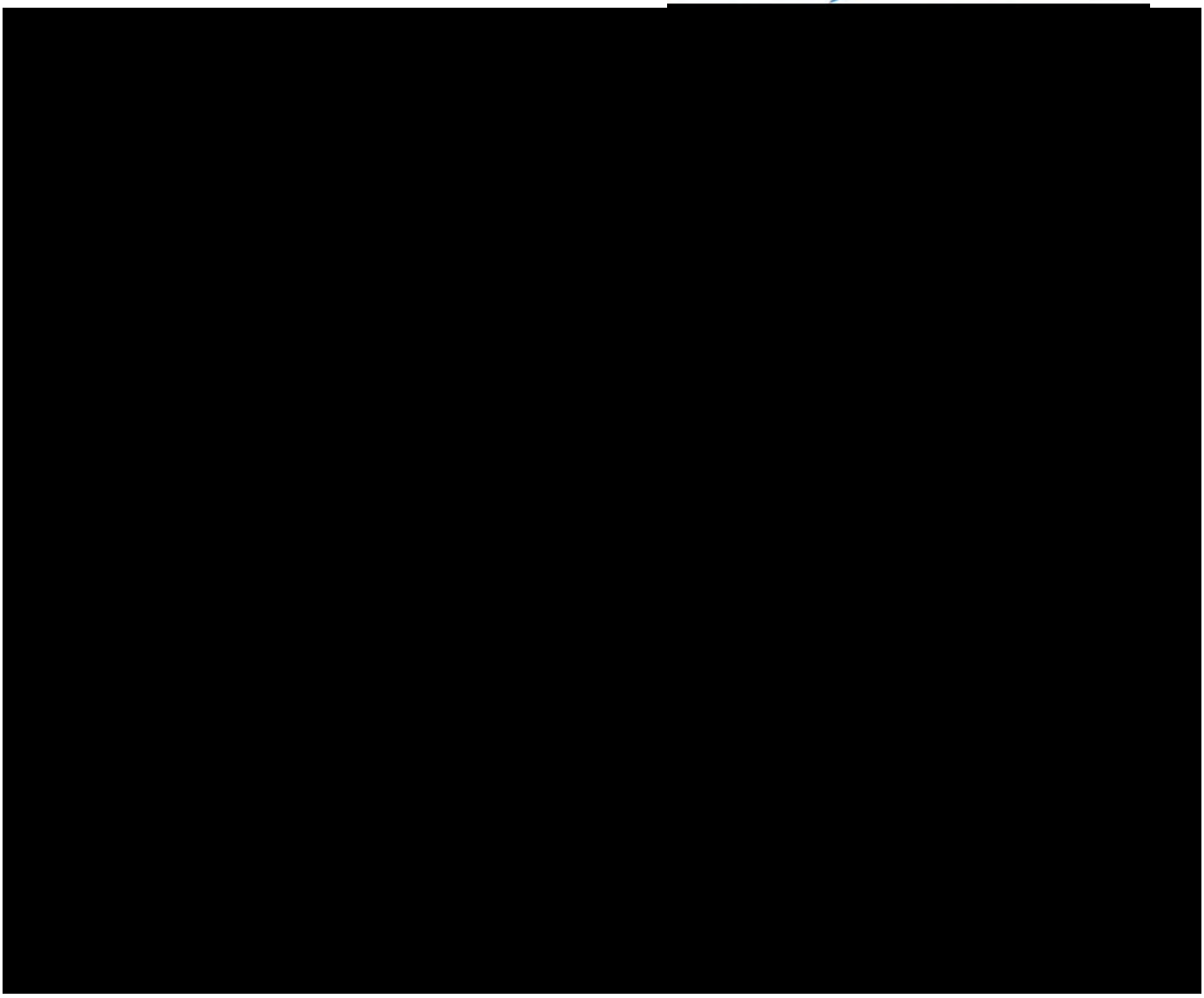
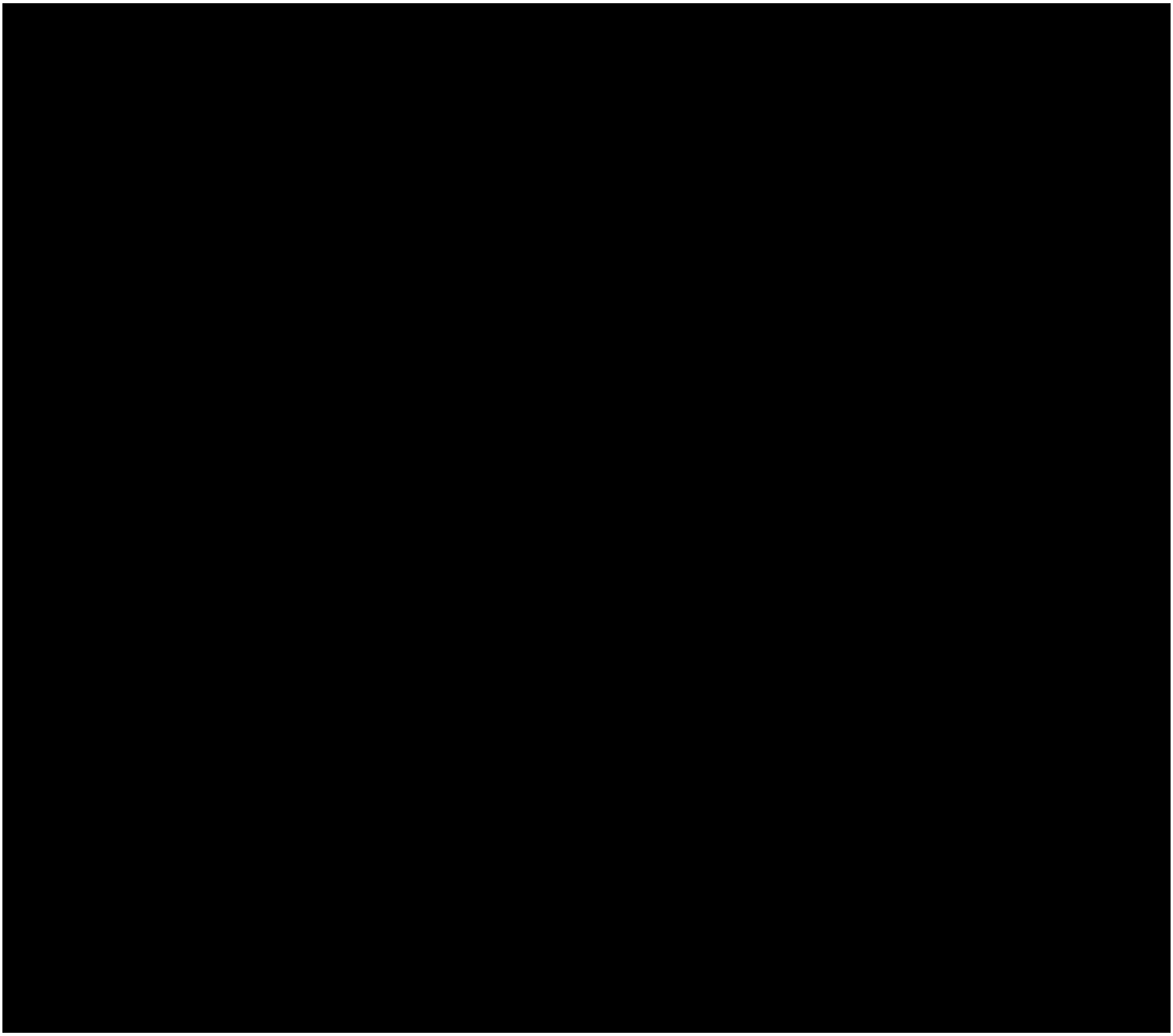
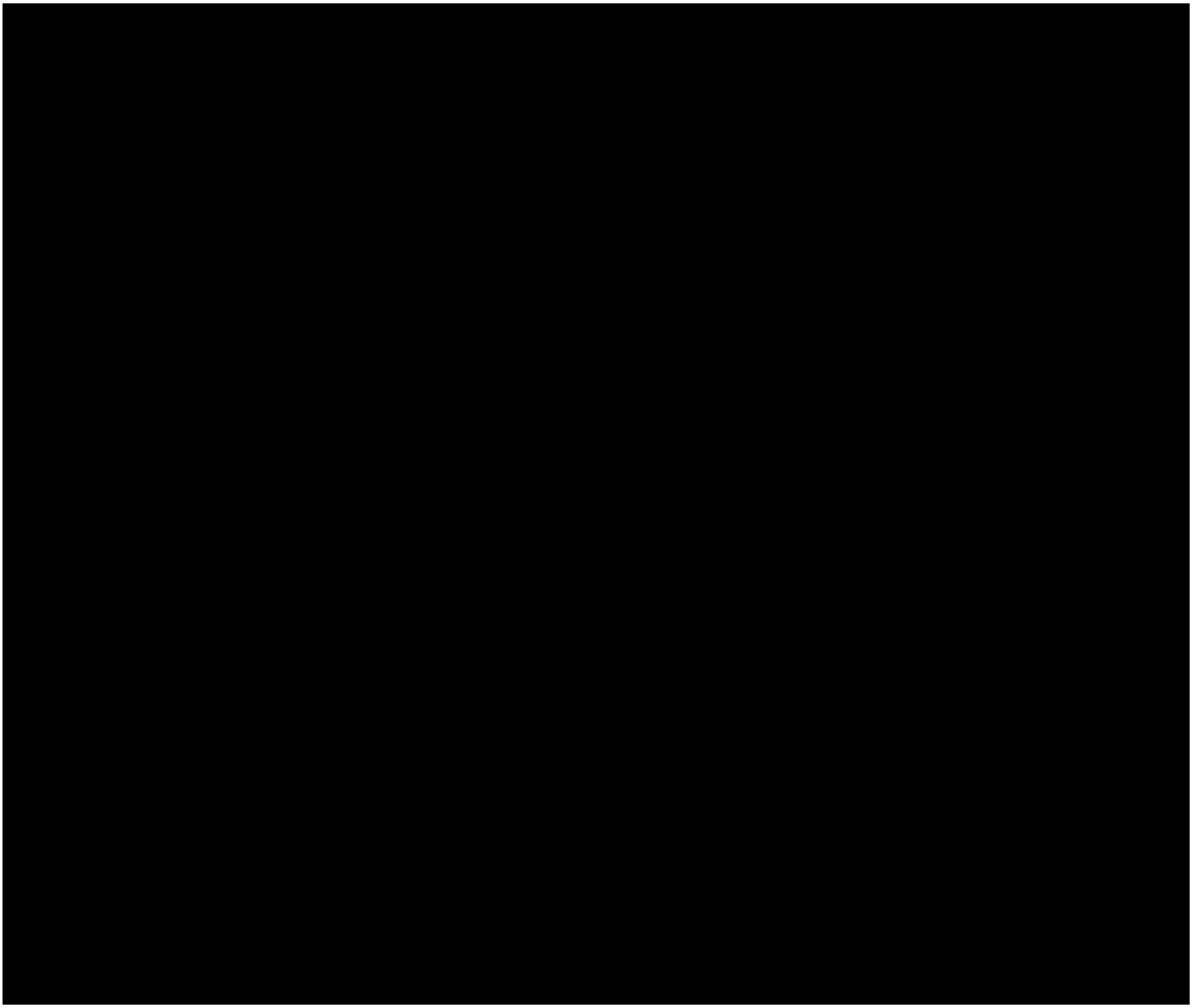
8.5.14 Baseline characteristics of MSM subgroups

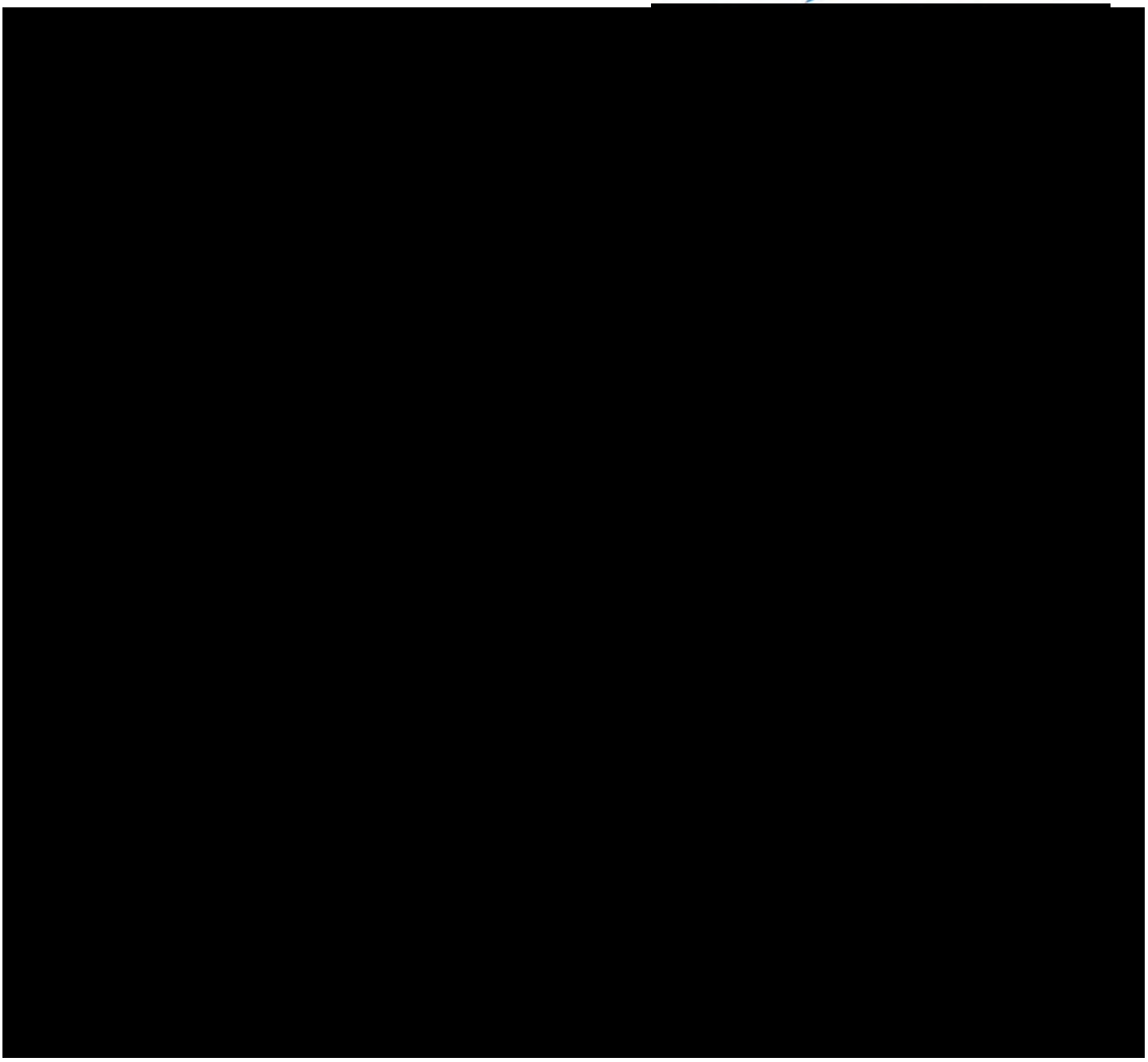






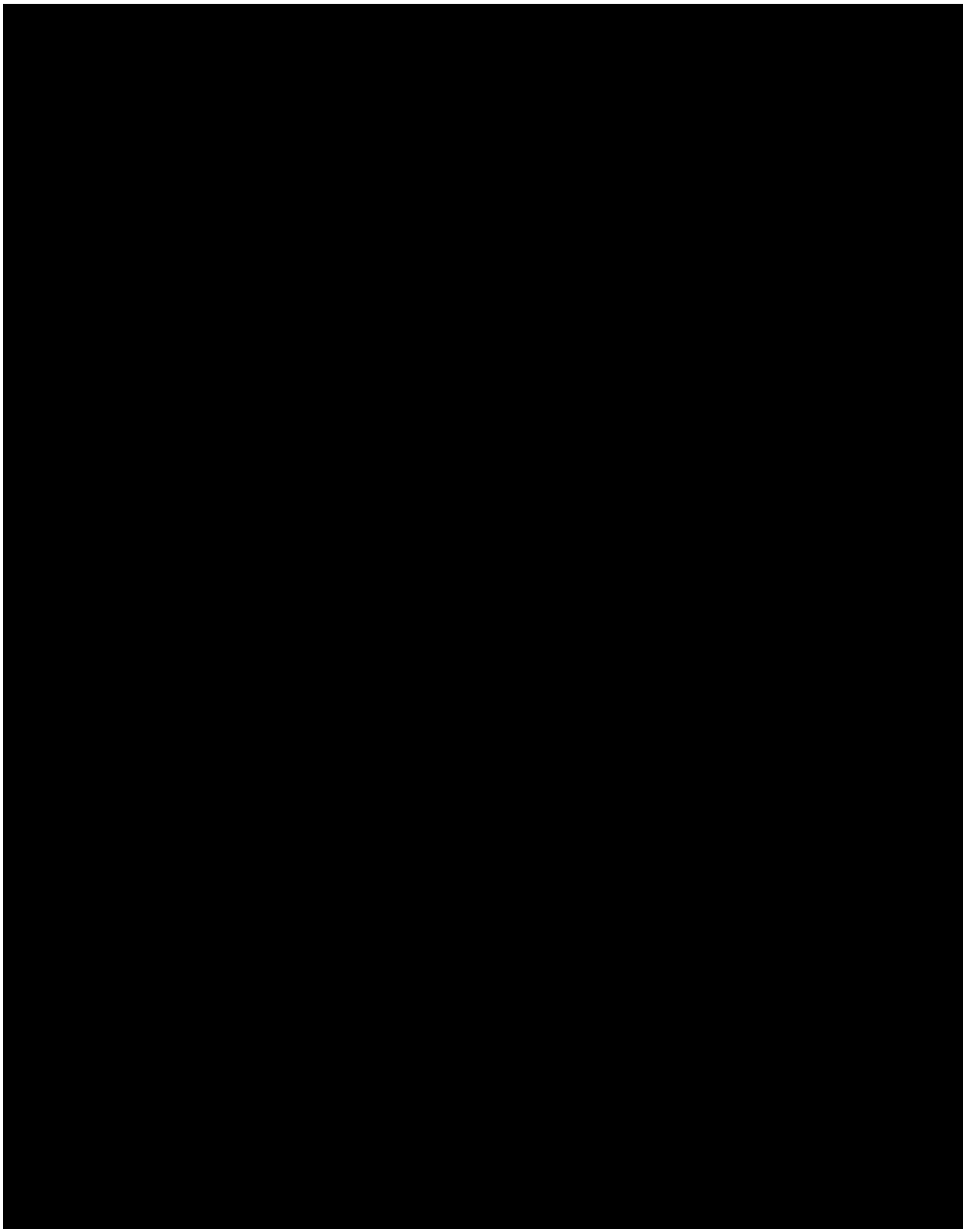


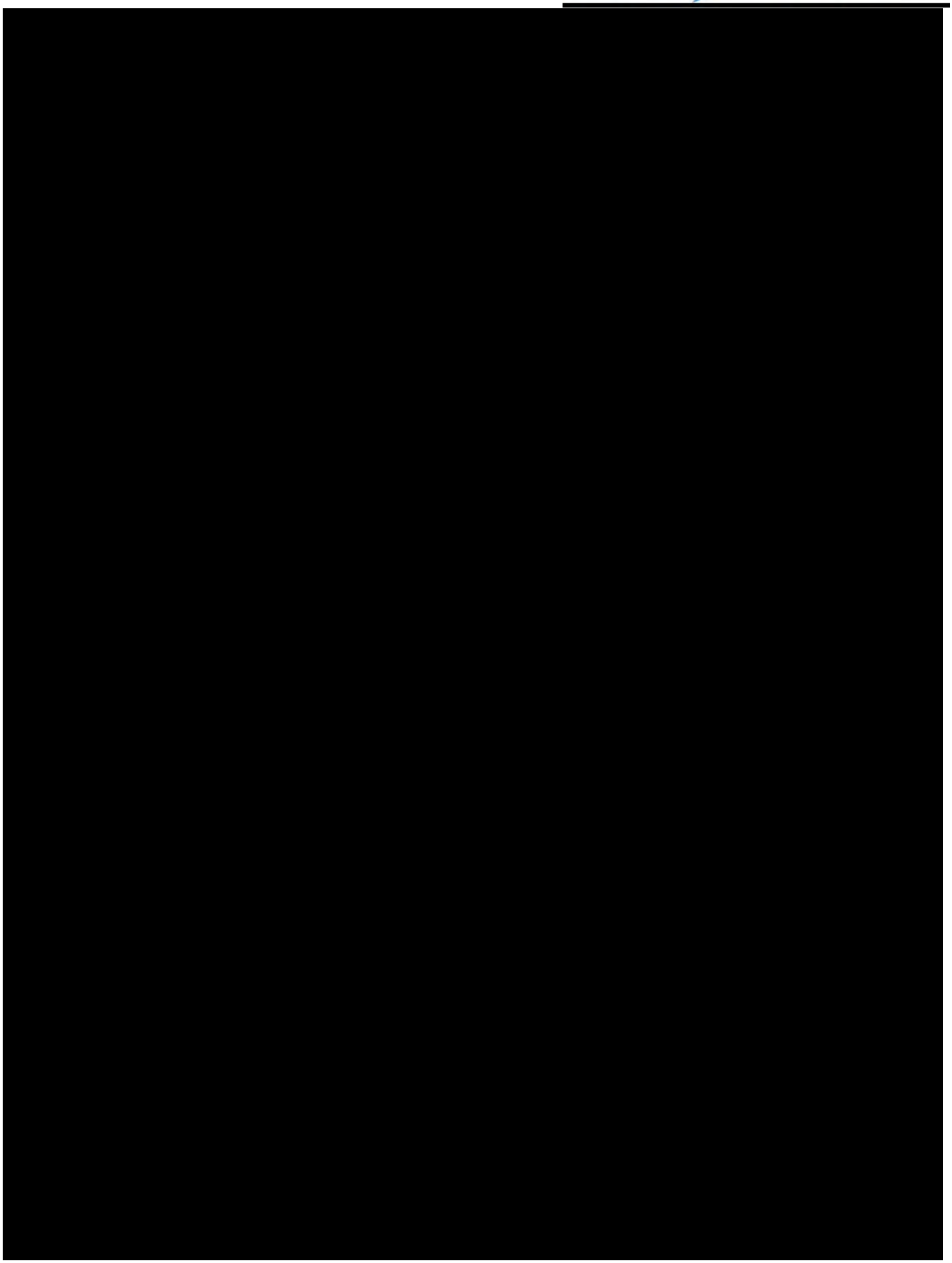




8.5.15 Baseline characteristics after weighting and histograms with the ATE (average treatment effect) weights

Table A5.33: Baseline characteristics after weighting for the full TRD population





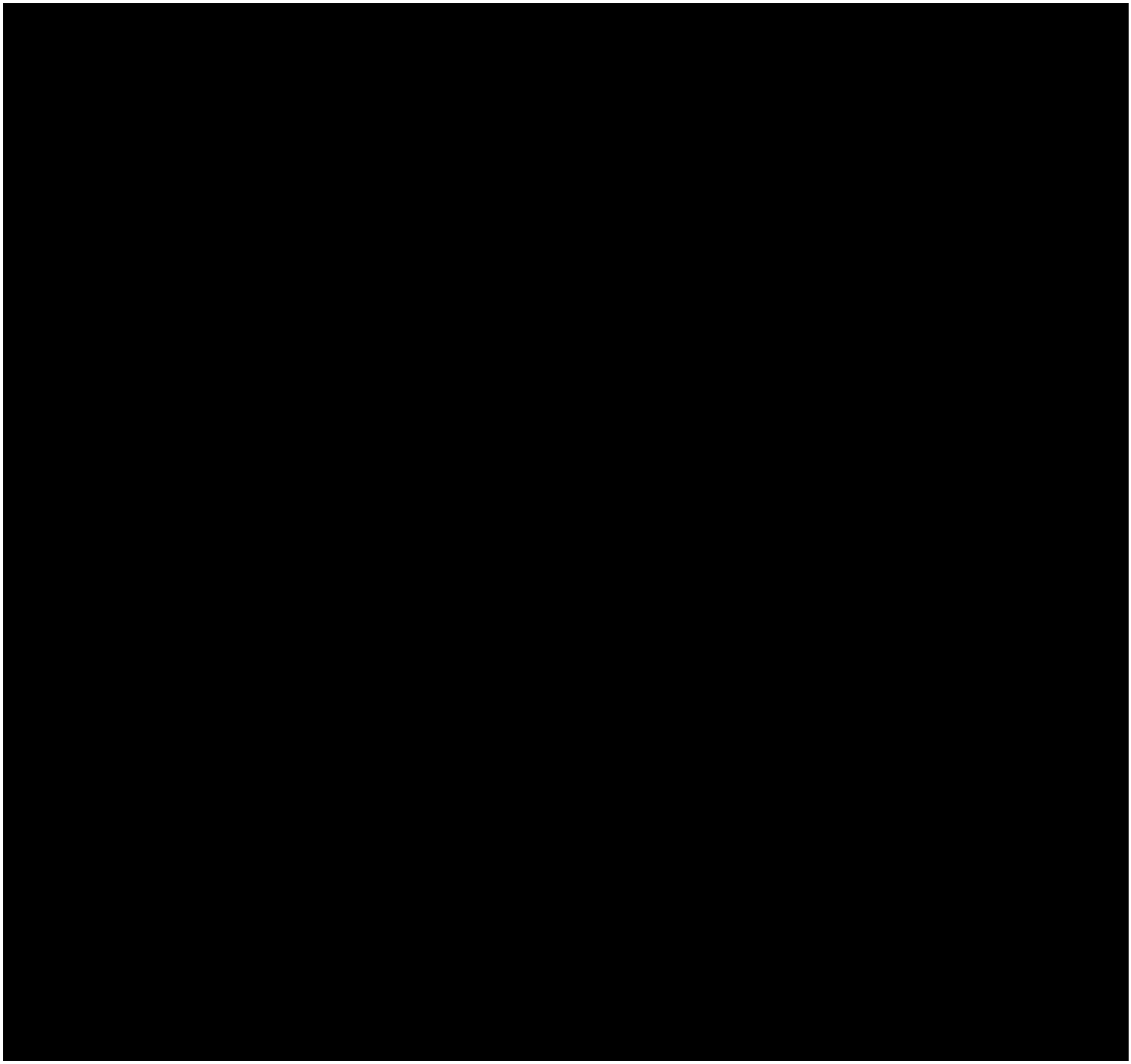
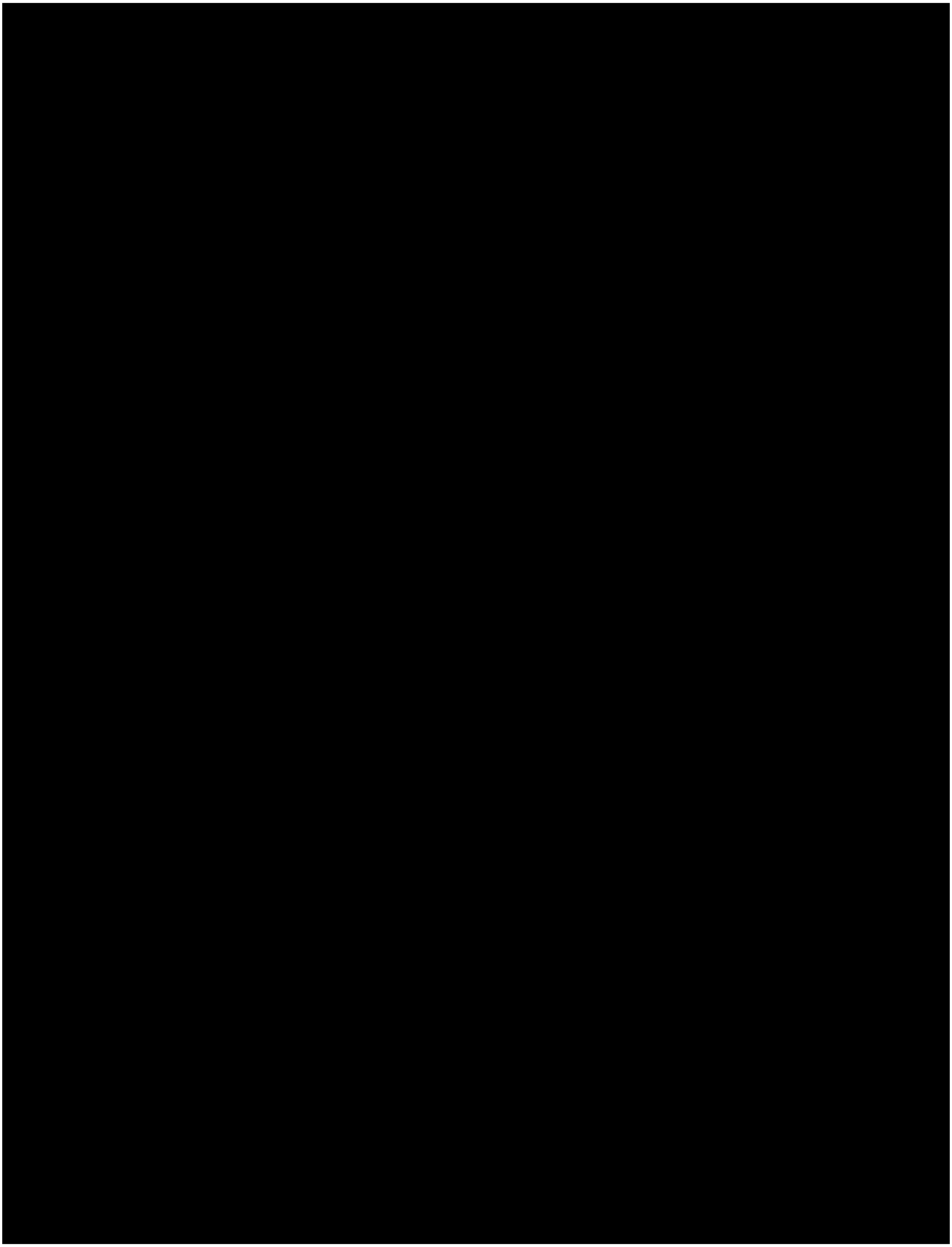


Table A5.34: Baseline characteristics after weighting for the MSM ≥ 7 subpopulation



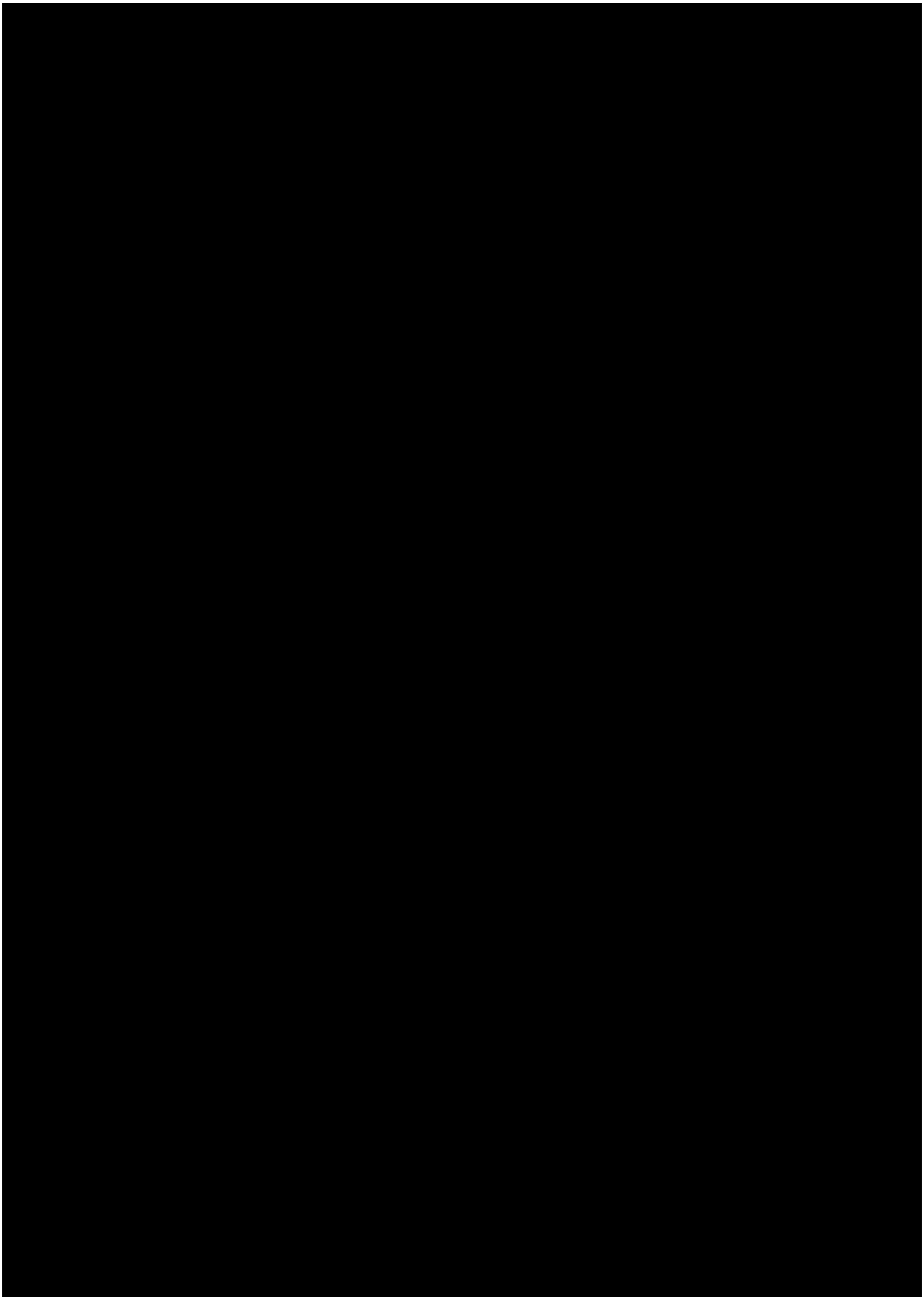
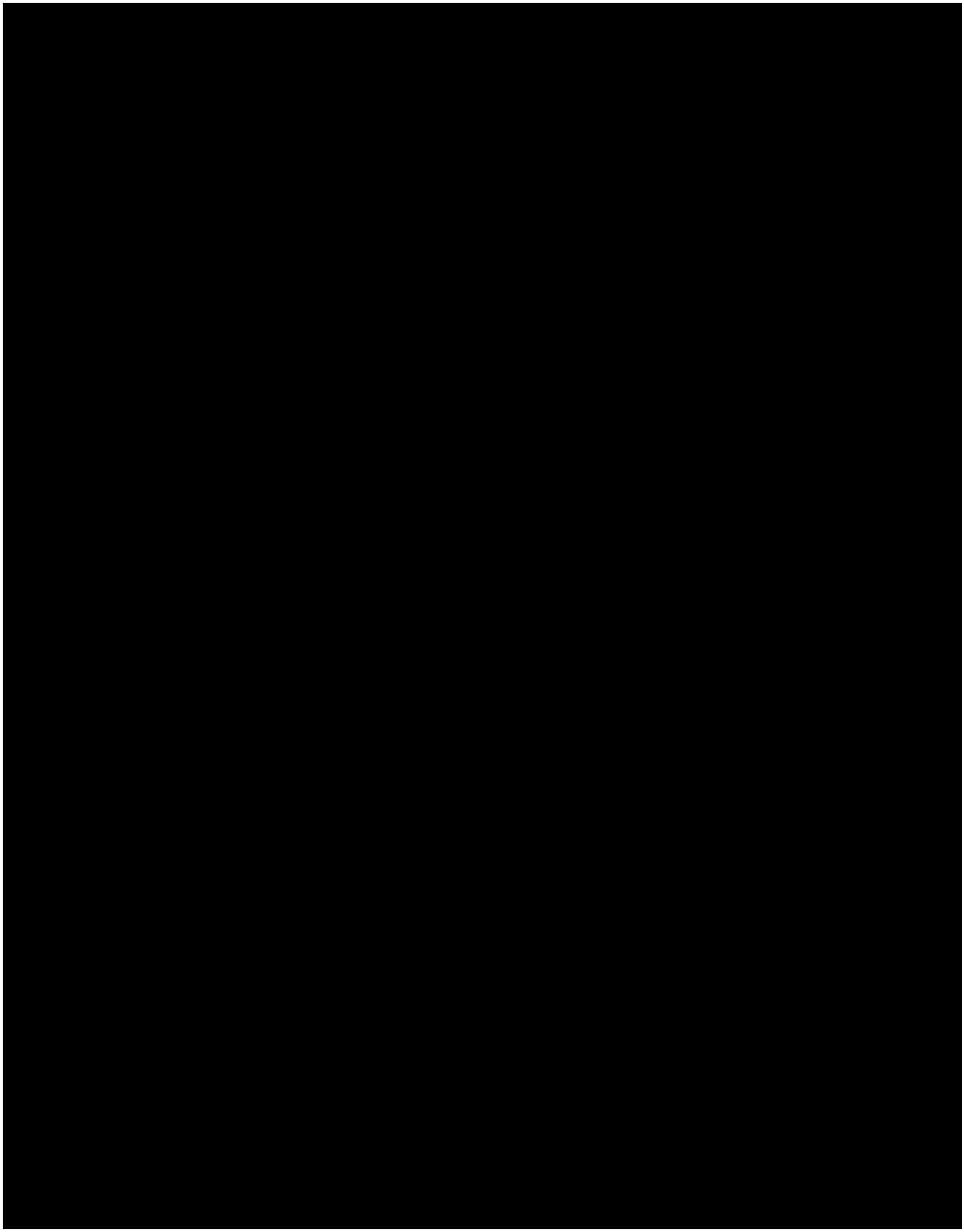


Table A5.35: Baseline characteristics after weighting for the MSM ≥ 8 subpopulation



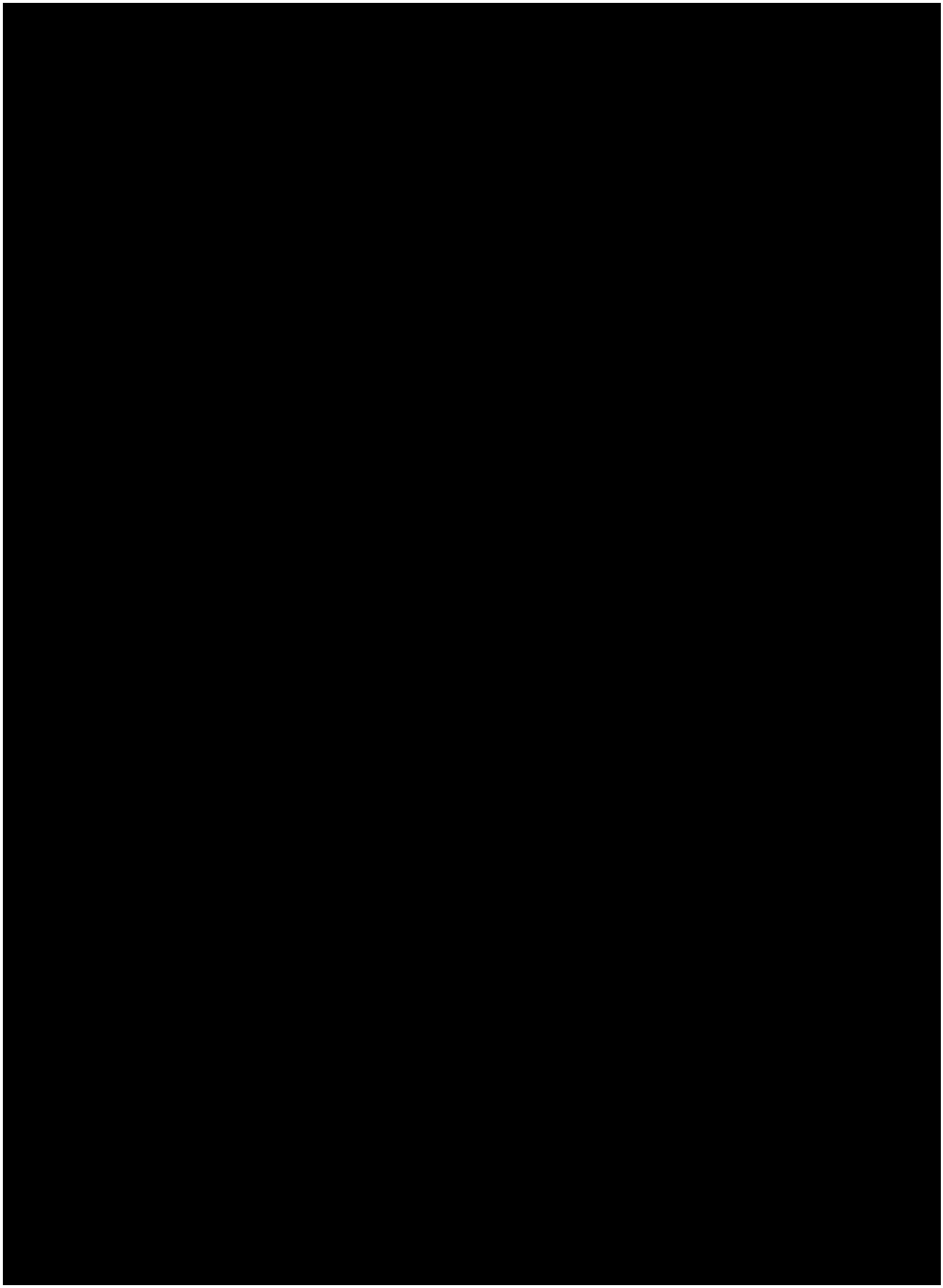
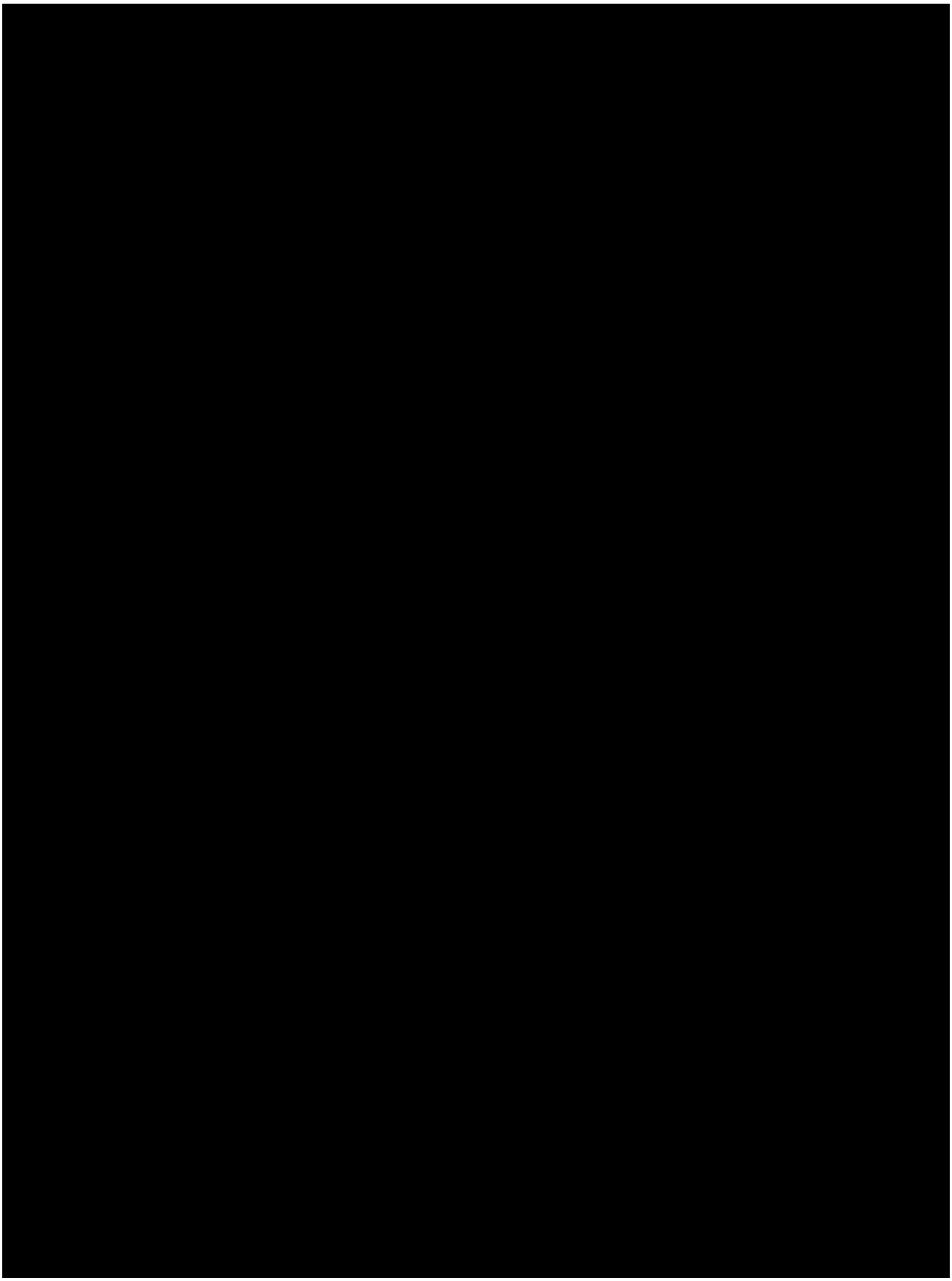
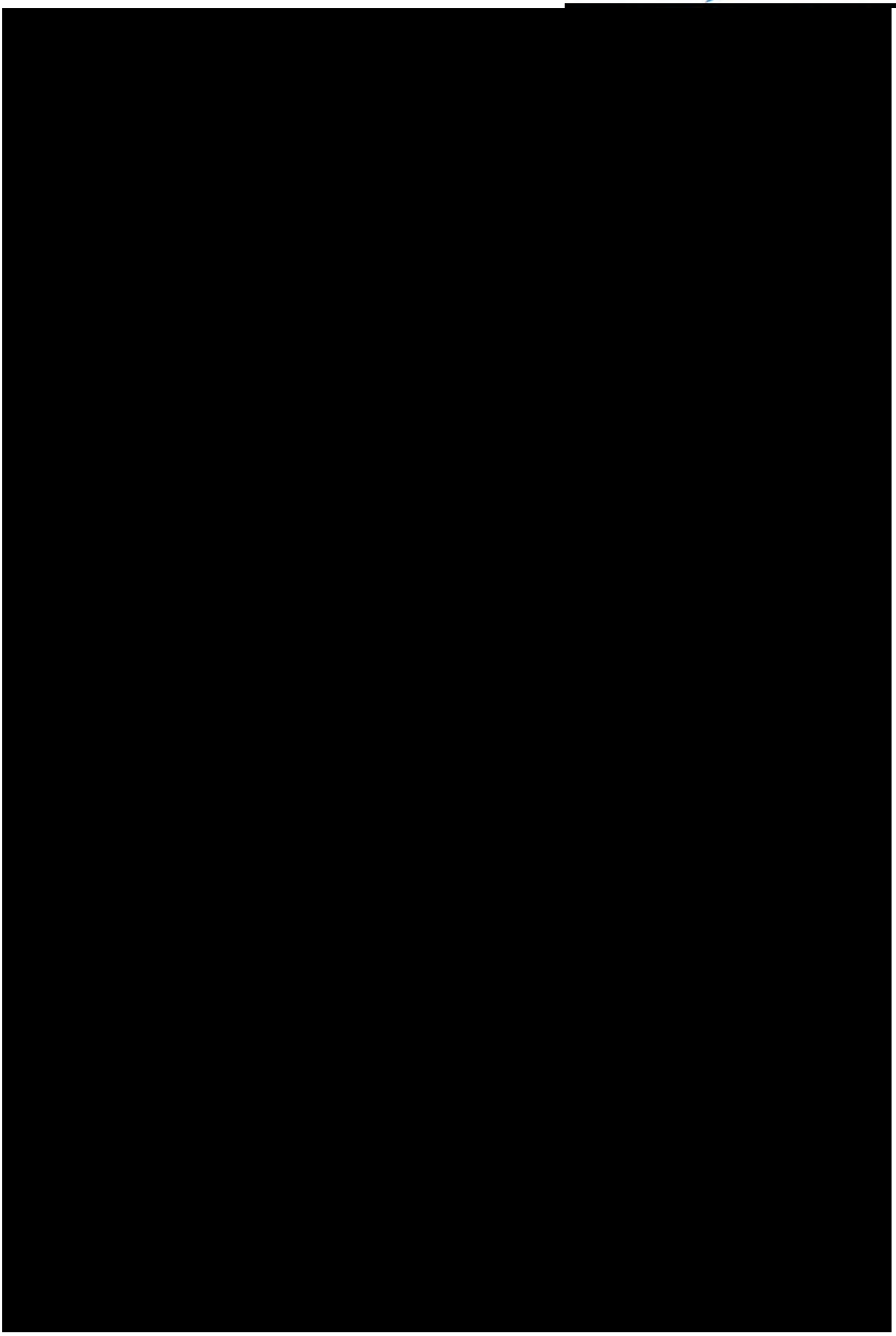


Table A5.36: Baseline characteristics after weighting for the MSM ≥ 9 subpopulation





8.5.16 Remission at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)

For the results in table A5.37 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.37: Percentage of subjects with remission (MADRS ≤ 10) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort.

8.5.17 Response at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)

For the results in table A5.38 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.38: Percentage of subjects with *response* (≥50% reduction from baseline in MADRS total score) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort.

8.5.18 Remission at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 7 population (clinical question 2)

For the results in table A5.39 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.39: Percentage of subjects with remission (MADRS ≤ 10) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 7 subpopulation.

8.5.19 Response at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 7 population (clinical question 2)

For the results in table A5.40 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.40: Percentage of subjects with *response* (≥50% reduction from baseline in MADRS total score) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 7 subpopulation.

8.5.20 Remission at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 8 population (clinical question 2)

For the results in table A5.41 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.41: Percentage of subjects with remission (MADRS ≤ 10) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 8 subpopulation

8.5.21 Response at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 8 population (clinical question 2)

For the results in table A5.42 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.42: Percentage of subjects with *response* (≥50% reduction from baseline in MADRS total score) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 8 subpopulation.

8.5.22 Remission at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 9 population (clinical question 2)

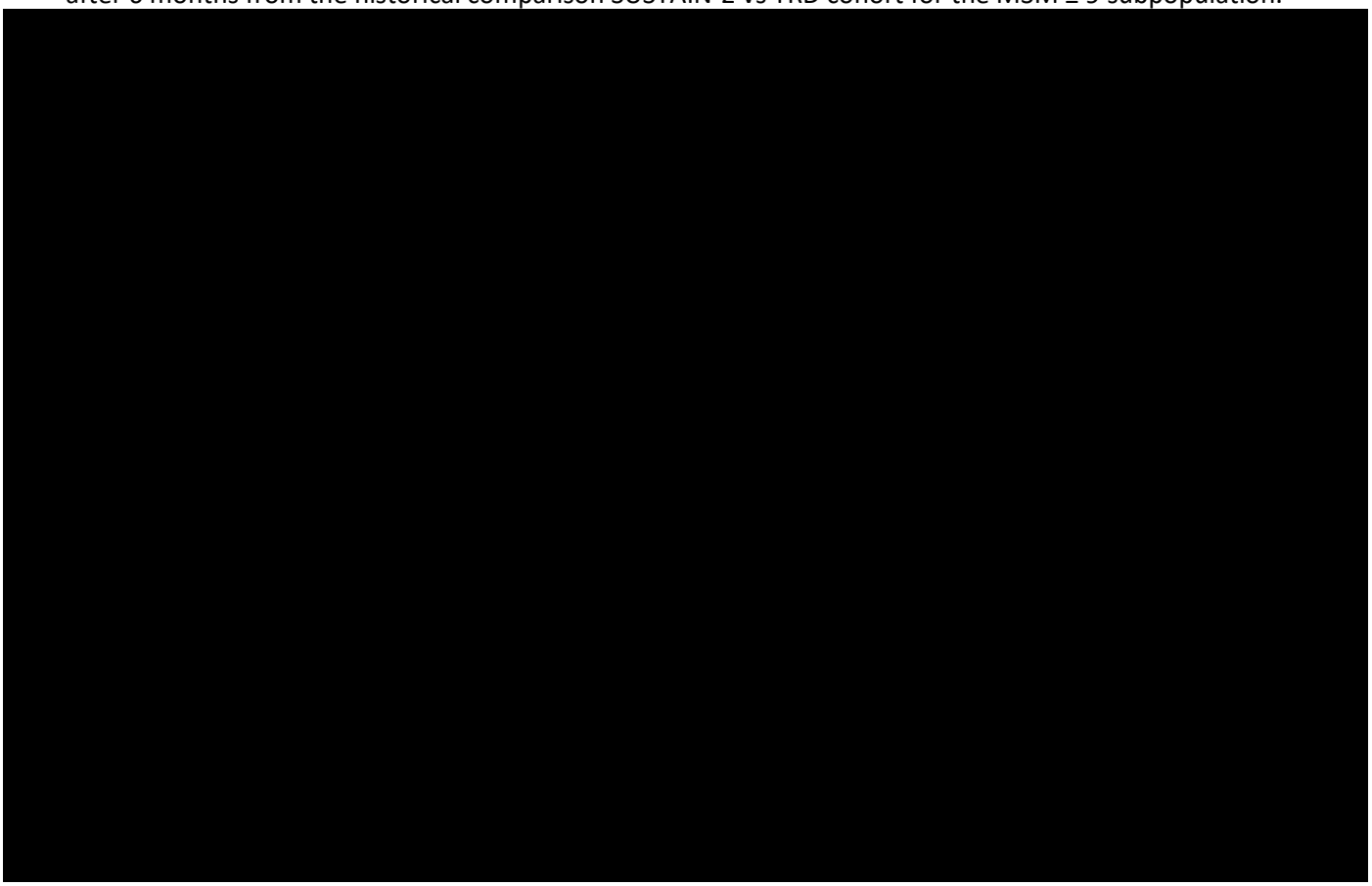
For the results in table A5.43 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.43: Percentage of subjects with remission (MADRS ≤ 10) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 9 subpopulation.

8.5.23 Response at 6 months with fNRI analysis approach – ITC of SUSTAIN-2 and the TRD cohort study for the MSM ≥ 9 population (clinical question 2)

For the results in table A5.44 a full non-responder imputation approach (NRI) was used for the binary endpoints in the event of missing data. In the SUSTAIN-2 study, full NRI was implemented in the main analyses for all patients that dropped out of the study (this includes all patients who stopped esketamine NS treatment) before reaching the Month 6 timepoint (Week 26). NRI was performed especially in the TRD cohort if (1) patients withdrew from the study before month 6, (2) patients had a change in treatment or treatment failure between baseline and month 6. In particular, discontinuation of treatment, switching treatment, initiation of combination treatment and augmentation were considered to be treatment failure.

Table A5.44: Percentage of subjects with *response* (≥50% reduction from baseline in MADRS total score) after 6 months from the historical comparison SUSTAIN-2 vs TRD cohort for the MSM ≥ 9 subpopulation.



8.5.24 MADRS total score at 6 months – ITC of SUSTAIN-2 and the TRD cohort study for the full TRD population (clinical question 1)

For the results in table A5.45 a full BOCF approach was applied on continuous outcomes that was consistent with the NRI approach applied on binary endpoint. For example, by imputing a MADRS score in BOCF when patients stop their treatment or discontinue the study, the patients satisfied the criteria for both non-remission (baseline score above remission threshold) and non-response (change from baseline = 0 implying relative improvement = 0%, ie, below the 50% threshold for response). The same patients were also imputed as non-responders and non-remitters with the NRI approach.

Table A5.45: Change in depressive symptoms according to MADRS total score from the historical comparison SUSTAIN-2 vs TRD cohort for full TRD population using full BOCF approach.

8.6 SUSTAIN-1 remission and response rates

The results presented for SUSTAIN-1 in table A6.1 and A6.2 are based on a partial Non-Responder Imputation (pNRI) approach where missing data is imputed as a negative outcome (non-response or non-remission depending on analysis) except if patients dropped out due to study termination (non-informative, kept as missing).

The population analysed consists of direct entry patients (excluding those transferred from TRD3001 or TRD3002) in the FAS IND population (having received at least one dose of ESK) with at least one post-baseline visit. Furthermore, pooled analysis of stable remitters and stable responders population are presented.

The results are only presented for the maintenance phase and timepoint of the analyses presented are only visits where less than 20% of patients dropped out due to study termination. In practice this means limiting the reporting of results to Week 14 of the maintenance phase (MA) in SUSTAIN-1.

Table A6.1 Proportion of patients with response (50% MADRS improvement) amongst the FAS population in the maintenance phase of SUSTAIN-1 utilizing partial Non-Responder Imputation (pNRI).

Table A6.2 Proportion of patients with remission (MADRS ≤ 12) amongst the FAS population in the maintenance phase of SUSTAIN-1 utilizing partial Non-Responder Imputation (pNRI).

8.7 SUSTAIN-2 remission and response rates

The results presented for SUSTAIN-2 in table A7.1 and A7.2 are based on a partial Non-Responder Imputation (pNRI) approach where missing data is imputed as a negative outcome (non-response or non-remission depending on analysis) except if patients dropped out due to study termination (non-informative, kept as missing).

Population consisted of direct entry patients (excluding those transferred from TRD3005) in the FAS IND population (having received at least one dose of ESK) with at least one post-baseline visit.

The results are presented for all treatment phase i.e. induction and optimization/maintenance. Timepoint of the analyses presented are only visits where less than 20% of patients dropped out due to study termination. In practice this means limiting the reporting of results to Week 26 of the optimization/maintenance phase in SUSTAIN-2.

Table A7.1 Proportion of patients with response (50% MADRS improvement) amongst the FAS population of SUSTAIN-2 utilizing partial Non-Responder Imputation (pNRI).

Table A7.2 Proportion of patients with remission (MADRS ≤ 10) amongst the FAS population of SUSTAIN-2 utilizing partial Non-Responder Imputation (pNRI).

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Cost-effectiveness Analysis for Esketamine in Treatment-resistant Depression in Denmark

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Table of Contents

Contents

List of Abbreviations

Abbreviation	Definition
AD	antidepressant
AE	adverse event
BP	blood pressure
CBT	cognitive behavioral therapy
CI	confidence interval
CPI	consumer price index
DSA	deterministic sensitivity analysis
ECT	electroconvulsive therapy
EQ-5D	European Quality of Life, five dimensions
EQ-5D-5L	European Quality of Life five dimensions, five levels
ESK	esketamine
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
HAM-D	Hamilton Rating Scale for Depression
ICER	incremental cost-effectiveness ratio
MADRS	Montgomery-Åsberg Depression Rating Scale
MADRS-S	Montgomery-Åsberg Depression Rating Scale-Self Report
MDD	major depressive disorder
MDE	major depressive episode
NHWS	National Health and Wellness Survey
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RR	relative risk
rTMS	repetitive transcranial magnetic stimulation
RW	real world
SD	standard deviation
SE	standard error
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SubTx	subsequent treatment
TRD	treatment-resistant depression
Tx	Treatment
WHO	World Health Organisation

1 Introduction

1.1 Disease Background: MDD and TRD

Major depressive disorder is a relapsing/remitting psychiatric disease characterized by recurrent depressive episodes. Treatment resistant depression (TRD) is defined as MDD that has not responded to treatment with at least two oral antidepressants in the current depressive episode.(1)
TRD is a severely debilitating and potentially life-threatening disease. Symptoms include profound sleep disturbance, fatigue, change in appetite/weight, agitation or slowness of speech/action, diminished concentration, decreased libido, inability to enjoy usual activities, and feelings of worthlessness. These symptoms result in an impaired capacity and inability to work, to the point of complete inability to function, which substantially interferes with social connection, integration and relationships. (2)
Symptoms of TRD may last for months or years. In many cases, patients with TRD feel weary of life or have suicidal ideation to the point of suicidal actions approximately 30% of patients with TRD attempt suicide at least once in their lifetime (3) Furthermore, TRD may develop at any age, but disproportionally affects people of working age which places a substantial burden on care givers and loved ones, the healthcare system, and broader society (4-7)

TRD patients typically suffer from an inadequate treatment response and cycle through numerous OADs primarily SSRIs and SNRIs as there is no single preferred agent for TRD in Danish clinical practice.(4, 8)
Despite the available pharmacological treatments, there is a serious unmet need for new and TRD specific treatments with a different mode of action since patients continue failing to achieve the overall treatment goal of remission and recovery with current treatment options. (9)

Designated as a Breakthrough Therapy by the US Food and Drug Administration and approved by the European Commission on December 19th 2019, Spravato® nasal spray is the first antidepressant specifically indicated for TRD. Based on the clinical trials included in the clinical part of the submission to the Medicines Council, data shows that flexible dosed Spravato® nasal spray, in combination with a SSRI or SNRI, provided statistically significant, clinically meaningful, rapid, and sustained improvement of depressive symptoms in patients with TRD versus placebo in combination with SSRI or SNRI. Furthermore, the extensive evidence on safety, including data from the SUSTAIN-2, SUSTAIN-3, SYNAPSE and ATU cohort report, provided in the clinical part of the submission underlines that Spravato in combination with an oral AD is a safe treatment. Furthermore, the new mode of action combined with the unique route of administration results in a rapid response (as early as 24 hours) and sustained long-term effect with clinical symptom improvement compared with currently available oral ADs.(10, 11)

Consequently, the recommendation of Spravato® in combination with a SSRI or SNRI, will provide danish TRD patients, who have failed at least two OADs or has a MSM ≥ 9 score, with the possibility to get a new innovative treatment which provides clinically meaningful, rapid, and sustained improvement of depressive symptoms and provides the first new opportunity in treatment for TRD in over 30 years. Subsequent improvements in a patient's quality of life will also likely have an additional positive impact on the lives of their careers, family and friends.

1.2 Esketamine nasal spray

Designated as a Breakthrough Therapy by the US Food and Drug Administration (FDA), esketamine nasal spray is the first antidepressant specifically indicated for TRD.(1, 12)

Esketamine is the S-enantiomer of racemic ketamine and provides the new mode of action in the treatment of TRD. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signaling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response. (1)

The dose recommendations for Spravato® are shown in Table A and Table B (adults ≥65 years). It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, Spravato® dosing should be individualized to the lowest frequency to maintain remission/response. After depressive symptoms improve, treatment is recommended for at least 6 months. (1)

Table A: Recommended dosing for SPRAVATO® in adults <65 years (1)

Induction phase	Maintenance phase
Week 1-4: Starting day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg twice a week	**Week 5-8:** 56 mg or 84 mg once weekly **From week 9:** 56 mg or 84 mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment	The need for continued treatment should be reexamined periodically

Table B: Recommended dosing for SPRAVATO® in adults ≥65 years (1)

Induction phase	Maintenance phase
Week 1-4: Starting day 1 dose: 28 mg Subsequent doses: 28 mg, 56 mg or 84 mg twice a week, all dose changes should be in 28 mg increments	**Week 5-8:** 28 mg, 56 mg or 84 mg once weekly, all dose changes should be in 28 mg increments **From week 9:** 28 mg, 56 mg or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment	The need for continued treatment should be reexamined periodically

Method of administration Spravato® is for nasal use only. The nasal spray device is a single-use device that delivers a total of 28 mg of esketamine, in two sprays (one spray per nostril). To prevent loss of medicinal product, the device should not be primed before use. It is intended for administration by the patient under the supervision of a healthcare professional, using 1 device (for a 28 mg dose), 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device. (1)

1.2.1 TRANSFORM Clinical Program

The clinical trials (TRANSFORM-2 and SUSTAIN-1) used to inform the health economic model are briefly described below. Data from TRANSFORM-2 and SUSTAIN-1 for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation will be utilized.(10, 11)

The clinical trial program for Spravato included 3 randomized, double-blind, phase 3 short-term studies evaluating the efficacy and safety of the drug during an induction phase (4 weeks) versus current standard therapy (SSRI / SNRI) in patients with treatment-resistant depression. The 3 short-term studies consisted of a fixed-dose study (TRANSFORM-1) and 2 flexible-dose studies (TRANSFORM-2 / TRANSFORM-3).(10, 13, 14) Fixed-dose studies meet specific regulatory requirements during a clinical trial program, but unfortunately do not allow individualized patient care. Therefore, the TRANSFORM-1 study does not reflect clinical practice, but may retain patients in inappropriate treatment. In contrast, flexible-dose studies allow individual treatment based on efficacy and adverse event profile.(13) Therefore, the 2 flexible dosing studies TRANSFORM-2 and TRANSFORM-3 are more suitable for assessing overall treatment with SPRAVATO during the induction phase.(10, 14) Since TRANSFORM-3 was performed in the elderly (≥65 years), which represents a smaller proportion of the total number of patients, it is best to use TRANSFORM-2, which includes patients from 18-64 years, to evaluate the induction phase in relation to clinical practice in Denmark. TRANSFORM-2 will be used in the health economic model for the acute phase.

1.2.2 SUSTAIN Clinical Program

According to the SmPC, the evidence of therapeutic efficacy at Spravato must be evaluated at the end of the induction phase to determine the need for continued treatment and that the continued treatment should be regularly re-evaluated during the maintenance phase.(1) The use of Spravato in the maintenance phase will therefore in Danish clinical practice reflect the criteria of the long-term study SUSTAIN-1, in which only patients with clinical response or remission should receive maintenance treatment with Spravato.(15) In addition, the baseline characteristics of enrolled patients in the SUSTAIN-1 study are consistent with the current patient profile of treatment-resistant depression in Danish regional psychiatry, in the case of patients with severe depression (mean MADRS score> 37 in SUSTAIN-1) of many years. duration (time since diagnosis ≥11 years) and where the current depressive episode is of longer duration (> 110 weeks in SUSTAIN-1), which has not been adequately treated with at least 2 prior antidepressants according to RADS current treatment algorithm for unipolar depression.(11, 16) Treatment with Spravato will therefore, despite common inclusion and exclusion criteria in the clinical studies, reflect the treatment of treatment-resistant depression in Danish clinical practice.

SUSTAIN-1 will be used in the health economic model for the maintenance phase.

2 Methods

2.1 Patients and Perspective

The economic evaluation includes adult patients (i.e., ages 18 and older) with a major depressive disorder (MDD) in Denmark, who have not achieved a clinically meaningful improvement after treatment with at least two AD agents, prescribed in adequate dosages and for adequate duration. This corresponds to clinical question 1 defined in the Medicines Council´s protocol for the evaluation of Spravato for TRD.

Furthermore, the economic evaluation includes the subpopulation of adult patients (i.e., ages 18 and older) with a major depressive disorder (MDD) in Denmark, who have not achieved a clinically meaningful improvement after treatment with at least two AD agents, prescribed in adequate dosages and for adequate duration, or had depression in to or more years (same episode) regardless of treatment and has a MSM ≥ 9 score. This corresponds to clinical question 2 defined in the Medicines Council´s protocol for the evaluation of Spravato for TRD. Only the results for the MSM ≥ 9 subpopulation will be presented in this economic evaluation dossier. However, the excel model includes the MSM ≥ 7 and MSM ≥ 8 subpopulation as these population are included in the clinical dossier but not defined by the Medicines Council as being part of clinical question 2.

The model population was 61.9% female with an average age of 46 (standard deviation [SD]: 11.89) years, as observed in the TRANSFORM-2 trial (10). The average MADRS score in TRANSFORM-2 at baseline was 37.1 (SD: 5.67), which signifies a severe depression (usually defined as a MADRS of 35 or above) (10).

The analysis was conducted using a restricted societal perspective as advised by in the Medicine Council´s methodology. (17) Consequently, irrespectively of whom the treatment associated expense was carried by, it was included with the exception of productivity losses. However, the analysis also includes the possibility of inclusion of productivity losses.

2.2 Treatment comparator and use of data

Janssen believes that Spravato® should be used as the first line treatment, and the Medicines Council have chosen the comparator in clinical question 1 of the application to be the oral anti-depressants SSRI or SNRI which currently are treatments used in the first line for TRD patients.(18) Data from the register-based study TRIDEN (Treatment Resistant Depression in Denmark) confirms that SSRI or SNRI is the standard first line treatment for TRD patients.(19)

However, Janssen acknowledge that there are different degrees of severity of TRD and therefore it is relevant to compare Spravato with oral anti-depressants SSRI or SNRI in such a subpopulation as defined by the Medicines Council in clinical question 2.(20)

2.2.1 Treatment comparator – 'Oral AD' comparator arm and efficacy data

In the model, the comparator arm, for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2), is a mix of SSRI and SNRIs used in clinical practice and in line with the Danish treatment recommendation for adult patients with unipolar depression, displayed in Table 1.(21) The inclusion of the specific SSRI and SNRI are based on the clinical trials. (10, 11, 13, 14) All patients were initiated, on one of four OADs from two classes: an SSRI (escitalopram or sertraline), or an SNRI (duloxetine or venlafaxine XR). Treatment with SSRI and SNRI is continuous and patients in long-term treatment with antidepressants (> 2 years) should be considered min. one time during the year with respect to whether treatment indication remains. (16)

An even market share distribution was applied as there is no standard of care (and no treatment specifically approved in this indication) for this population. This assumption only impacts the drug acquisition costs, but as they are similar for all oral ADs the distribution in market share does not have a big impact on the results.

For simplicity this arm is called the 'Oral AD' comparator arm. As there is no standard of care, none of these sources model treatment efficacy at the individual agent level, instead the sources include a mix of oral ADs.

Table 1: Mix of oral ADs (used in the 'oral AD' comparator arm)

Comparators	Drugs	Market share
'Oral AD'	Duloxetine	25%
	Escitalopram	25%
	Sertraline	25%
	Venlafaxine	25%

2.2.2 Limitations of using the clinical trial data as a source of efficacy in the comparator arm

There are several limitations in using data from the active comparator arm in the clinical trials (TRANSFORM- 2 and SUSTAIN-1), which impacts the applicability to clinical practice. These limitations are further described in Appendix B. Alternative sources have been provided.

This is summarised below:

Acute phase

- The placebo effect in clinical trials in depression is well-documented and is the reason for high failure rates due to not being able to reach statistical significance (22, 23)
- The response and remission rates for placebo nasal spray plus oral AD from TRANSFORM-2 are high compared to other studies in depression (9, 24, 25)
- The high number of healthcare visits (due to the nasal spray administration) and the use of a placebo nasal spray are unlikely to reflect clinical practice for oral AD treatment (23, 26-28)

Maintenance phase

- Although considered appropriate to inform the esketamine nasal spray plus oral AD group of the model, the randomized blinded withdrawal design of SUSTAIN-1 trial might present uncertainty regarding the expected relapse risk for oral ADs. This is due to the inclusion of an optimization phase in SUSTAIN-1, in which patients first received esketamine nasal spray plus oral AD and achieved stable remission, prior to being randomized to either continue esketamine nasal spray plus oral AD or to receive placebo nasal spray plus oral AD. (11) As a result, the effect of the withdrawal of esketamine nasal spray plus oral AD may have been carried over to the subsequent placebo nasal spray plus oral AD.
    - An indirect treatment comparison of SUSTAIN-2 and the TRD cohort has been utilized, in the clinical part of the submission to the Medicines Council.(29, 30) This was to provide long-term comparative response and remission data for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). However, these results are not utilized to inform the health economic model, as the model after the acute phase, is driven by relapse/loss of response rates. These relapse/loss of response rates are only available from the SUSTAIN-1.

3 Health economic analysis and model

3.1 Health economic analysis

A CUA was conducted with the objective of comparing esketamine nasal spray plus oral AD with oral ADs in the treatment of patients with TRD who have not responded to at least two antidepressants as well as patients with TRD who have a MSM ≥ 9 score. 'Oral AD' comparator arm in the model is used a collective word to describe the modelled TRD comparator arm.

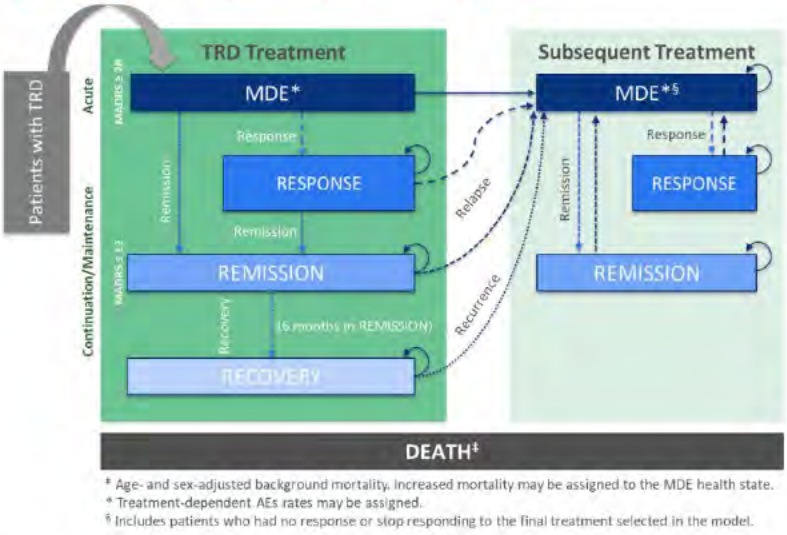
3.2 Model structure

Base case model

A Markov cohort model was developed in Microsoft Excel® to track the disease progression and costs experienced by the patient's cohort throughout the model time horizon. The model reports health outcomes, including life years, quality-adjusted life years (QALY), direct and indirect cost outcomes.

The model (Figure 1) is built to take into consideration esketamine nasal spray treatment during the current depressive episode. The patient cohort enters the model in the acute phase with an MDE, having failed to achieve a clinically meaningful improvement after treatment with at least two AD agents, prescribed in adequate dosages for adequate time (TRD population). Furthermore, the cohorts that enters the model can be chosen to be the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulation. The cycle length of the model is 4 weeks.

Figure 1. Markov Cohort Model Flow Diagram



The base case model includes one treatment course of esketamine nasal spray or the 'Oral AD' comparator arm within one depressive episode. Patients who are non-responders, who lose treatment response, who relapse or have a recurrence will transition to a pre-defined subsequent treatment.

As there is no standardized treatment pathway for patients who do not achieve a sufficient response with standard oral AD treatment (SSRI/SNRI) it is assumed that all patients will move to the same mix of treatments.

Re-treatment scenario model

Janssen has, in addition to the base case model, incorporated the possibility to conduct a Spravato re-treatment scenario analysis. This option was incorporated, as the Medicines Council has as part of the validation process requested Janssen to incorporate an option in the model to choose a scenario where a patient can receive re-treatment with Spravato before moving on to subsequent treatment. The request was based on the Expert Committee stating that if a patient has benefitted from treatment with Spravato earlier on, they would initiate treatment with Spravato again in the event of a relapse/recurrence. We refer to appendix D for the results of re-treatment scenario model, limitations of the model and argumentation on why the base case model should be used be used considered the most appropriate model for the health economic evaluation.

3.2.1 Model Health States

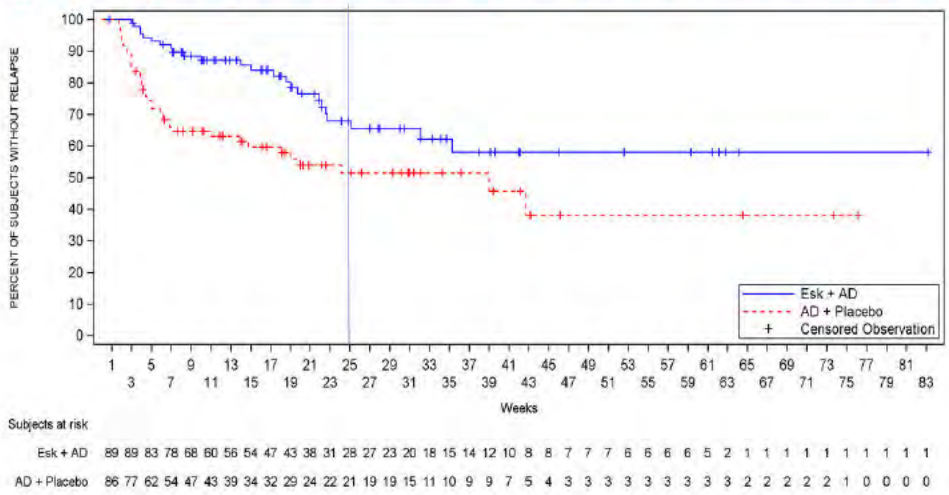
The health states used in the model are based on the definitions used in the clinical trials and are commonly used to describe the disease progression.

The health state definitions are described below:

- Response: defined as ≥50% improvement from baseline in the MADRS score (excluding those patients who achieve remission)
- Remission: a patient is considered to achieve remission when their MADRS score is ≤12
- Recovery: a patient who has stayed in uninterrupted remission for 36 weeks (approximately 9 months)

In this model, the recovery timepoint is 36 weeks of relapse-free remission and indicates a state where the risk of relapse is lower. This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The 36-week definition (for recovery definition) was supported by clinical data on relapse among stable remitters from SUSTAIN-1(11). After 24 weeks of maintenance therapy, patients from both treatment arms showed a reduced risk of relapse, see figure 2. This corresponds to 36 weeks after the acute treatment period (12 weeks optimisation + 24 weeks maintenance). Thus, patients before this timepoint are in remission and are subject to higher relapse risk compared to patients who had passed 36 weeks post-acute treatment, where their relapse risk is lower.

Figure 2. Relapse Kaplan-Meier Curves - Maintenance Phase from SUSTAIN-1 for stable remitters



The following definitions are used for the transitions between health states:

- Loss of response: worsening of symptoms and return from response to the MDE health state
- Relapse: worsening of symptoms and return from remission to the MDE health state
- Recurrence: indicates a return of symptoms (after reaching recovery) and entering a new depressive episode.

3.3 Model time horizon and treatment schedule

The time horizon for the base case is five years, as a shorter time horizon is not appropriate for TRD patients and it would not fully capture the health benefit of esketamine nasal spray plus oral AD. This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Traditionally health economic models in depression have a model time horizon of 1 year, which may be appropriate when assessing a mild depression where a depressive episode normally lasts 3-6 months. However, for patients who reach TRD status have a history of many years with a depression diagnosis and several previous episodes. It is well-documented that the length of an episode tends to increase with an increased number of previous episodes. In the TRANSFORM-2 trial the average length of the current episode was 111 weeks (with an average duration of 12 years since their first depression diagnosis).

Treatment of depression refer to two main phases: acute and maintenance where initial treatment aims to stabilize symptoms and get the patients into remission (and return to normal function) while the latter is focused on preventing relapse. The esketamine nasal spray SPC includes a dosing schedule, table 2, which is based on the schedule followed in the clinical trials(1).

Table 2: Esketamine nasal spray treatment schedule (SPC text)

Induction Phase	Maintenance Phase
Weeks 1-4: twice weekly	Weeks 5 8: once weekly

Induction Phase	Maintenance Phase
Starting Day 1 dose*: 56mg Subsequent doses: 56mg or 84mg	56mg or 84mg **From Week 9: once weekly or every second week**** 56mg or 84mg *
Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment.	Periodically reexamine the need for continued treatment.

It is recommended that for those patients where symptoms have improved, treatment with esketamine nasal spray should continue for at least 6 months. In the health economic model, it is assumed that patients who discontinue esketamine nasal spray will continue their oral antidepressant as a preventative treatment.(1) This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

3.4 Treatment phases

3.4.1 Acute phase

In the acute treatment period (i.e., the first 4 weeks), patients can end up in three main health states (MDE, responder, remission) or die. Response and remission are evaluated at the end of the 4-week acute treatment period, although it is possible that some patients may experience treatment benefits that would allow them to be classified as responder or remitter before reaching the end of the acute period. The 4-week timepoint is consistent with the primary endpoint from TRANSFORM-2. This affects all comparators in the same manner and allows for simplifying the model.

At the end of the 4 weeks, it is recommended that the therapeutic effect is evaluated to confirm the need for continuous treatment. In TRANSFORM-2, 30% of the full TRD patient population and [redacted] of the MSM ≥ 9 subpopulation did not achieve a response (≤ 50% reduction on the MADRS scale), at this timepoint and would therefore discontinue esketamine nasal spray as it is unlikely that they will progress with continued treatment.

Patients who discontinue esketamine nasal spray due to all-cause drop-off risk (lack of response or AEs) is assumed to stay in the MDE health state. Patients who do not reach response (fail to respond) or remission (or experience AEs) after the first 4 weeks and hence remain in the MDE health state, will start the next treatment in the sequence (subsequent treatment mix described in section 4.5.1).

The treatment effect in the acute phase for esketamine nasal spray plus oral AD and the active comparator arm is sourced from TRANSFORM-2.(10) However, it is important to be aware of the limitations of the data for the active comparator arm in TRANSFORM-2 (described in section 10).

3.4.2 Maintenance phase

The maintenance phase is divided into two parts: optimization and maintenance to reflect the trial design (and recommended treatment schedule) where the esketamine nasal spray treatment frequency is reduced in week 9-40 (see section 3.3). In the maintenance phase, patients can remain in the same health state, improve and move onto the next health state or move back to the MDE health state due to loss of response/ relapse (symptom worsening in remission). One additional health state of recovery is added in the maintenance phase and is based on time spent with relapse-free remission, which is assumed to be

after 36 weeks. The recovery health state is addressing the fact that the risk of relapse decreases over time and that the difficulty of capturing time-varying risks in a Markov approach. In remission, patients experience a constant risk of relapse that is higher than the constant risk of recurrence for patients in recovery.

The maintenance phase continues until all patients have stopped esketamine nasal spray (due to re-entering the MDE health state, discontinuing treatment, entering recovery and subsequently stop or die). Patient who remain on treatment will continue to cycle through the health states. Patients who have entered the recovery health state can remain in recovery and discontinue esketamine nasal spray at defined time points (see section 3.5 Discontinuation) or experience a recurrence (and enter a new episode, i.e. MDE health state).

The treatment effect in the maintenance phase for esketamine nasal spray plus oral AD is sourced from SUSTAIN-1 in the base case analyses. However, due to the limitations of the data for the active comparator arm in SUSTAIN-1 (described in section 2.2.2), an alternative source have been provided for these transition rates (described in section 4).

The assumptions described above is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

3.4.2.1 Subsequent treatment

Patients who experience a worsening of symptoms will start the subsequent treatment. The model is built in line with the esketamine nasal spray label where a patient would need to fail two oral antidepressants in the current depressive episode (to be defined a treatment resistant). Hence, if a patient experiences a recurrence (i.e. a new depressive episode) this patient will be treated with the subsequent treatment (subsequent treatment mix). This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Patients may still achieve response or remission at every cycle, as well as experience relapses, in which case they transition back to the MDE health state where they again have a chance to achieve remission or response.

3.5 Discontinuation

The discontinuation rates are comparator- and treatment phase-dependent, and independent of prior lines of treatment. The number of patients who are receiving treatment in each cycle is calculated as the number of patients in the health state minus the number of patients who had discontinued in that health state.

3.5.1 Discontinuation in the acute phase

In the acute phase no discontinuation was allowed for either of the treatment arms. After the acute phase (4 weeks of treatment) the patients who were non-responders in TRANSFORM-2 discontinued esketamine nasal spray. This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

3.5.2 Discontinuation in the maintenance phase

In the maintenance phase, patients discontinued esketamine nasal spray due to experience of adverse event, loss of response, relapse and death. All patients, while in the response health state continue to receive esketamine nasal spray in order to prevent relapses, which is supported by evidence from SUSTAIN-1 where stable responders who switched to placebo nasal spray plus AD had a higher risk of relapse compared with the stable remitters (57.6% vs 45.3%, full TRD population).(11) This is believed to be due to a more vulnerable patient group who are at a higher risk of relapses, which is also supported by physicians.

For those patients who achieve recovery, it is expected that they will discontinue esketamine nasal spray when there is no clinical need for further treatments (clinical evaluation recommended after 6 months and the ongoing). In clinical practice, it is expected that physicians would aim to reduce the esketamine nasal spray treatment length as much as possible. But as TRD patients have a severe depression (long time since first diagnosis and long/recurrent episodes), it is expected that the majority of patients will require esketamine nasal spray treatment for 6-12 months with a small proportion of patients who will require up to 24 months. In the model, 9 months (approx. 36 weeks) is defined timepoint of recovery, hence this is the first time a patient is allowed to stop esketamine treatment. This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

After discontinuing esketamine nasal spray, the patient will remain on oral AD treatment to prevent recurrence for the remainder of the time horizon (unless they experience a recurrence or die).

Discontinuation assumptions for esketamine nasal spray in recovery are supported by the following evidence:

- The SPC text of esketamine nasal spray (and other AD treatments), recommends that treatment should be maintained for at least 6 months after depressive symptoms are improved.(1)
- Danish guidelines for the treatment of unipolar depression recommend AD treatment for at least 6 months or longer (up to 2 year in order to further prevent relapses), if there has been one or more depressive episodes in the past or if other risk factors for relapse are present.(8)
    - Similarly, guidelines from the Swedish MPA recommend AD treatment for at least 6 months or longer (up to 1 year in order to further prevent relapses). They also recommend that after this period, treatment is gradually discontinued (31) .
    - Similarly, the National Institute for Health and Care Excellence (NICE) guidelines for depression indicate that, for relapse prevention, patients should continue ADs for at least 6 months after remission. However, for patients at high risk of relapse, ADs should be continued for at least 2 years (32).
- The average episode length in the TRANSFORM-2 trial was 111 weeks.(10)
    - Approximately 35% of the patients in the TRANSFORM-2 trial had fewer than 2 episodes and could indicate a lower risk of relapse.

3.6 Mortality

From all health states, patients may die as defined by age- and sex-adjusted all-cause mortality. In addition to the background mortality, TRD is associated with additional suicide related mortality. TRD is a life-threatening disorder, and approximately 30 % of patients with TRD attempt suicide at least once during their lifetime (33). The overall incidence of completed suicides was 0.47 per 100 patient years and was captured in the model for the MDE health state. Patients in response state experienced half of the completed suicide risk in MDE state (Expert statements 2019). Overall completed suicide rates reported for patient with TRD were added to the background mortality for patients at MDE and response states. These rates were used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). Both applied estimates were likely to be conservative (i.e., not benefitting esketamine), since the additional suicide risk in the MDE state is likely to be higher than in the TRD generally. Remission and recovery had no impact on the mortality (Expert statements 2019)

In the base case, 30% of patients with TRD attempt suicide at least once during their lifetime (33).

3.7 Utility and QALY Calculations

3.7.1 Health State Utilities

The utilities are stratified by health state. The health state QALYs at each cycle are calculated by multiplying the user-specified utility by the number of patients in each health state at each cycle. The utilities for each health state were based on DK weights published by Jensen et al. 2021.(34) For further description see section 5.3.

3.7.2 AE-associated Utility Decrement Calculations

For each AE included in the model, treatment-dependent inputs are used to calculate the associated utility decrement by treatment: the incidence for each AE by treatment, the duration of each event, and the utility decrement of each event. The per-cycle utility decrement is calculated for all AEs and then summed to give a per-cycle AE-associated utility decrement for each treatment. This decrement is added to the utility only for patients on treatment during the acute phase; it is assumed that patients who are not on treatment do not experience any AEs. AEs associated with treatment are assessed only in the acute treatment phase and not in the maintenance phase, as it is assumed that patients are likely to have adapted well to the treatment by this time. This assumption is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

The inclusion of AE-associated utility decrement is likely a conservative assumption, as the impact of AE on quality of life may already be captured in the utility analysis for the health states. Thus, the inclusion of AE-associated utility decrements may be double counting the impact of AEs on quality of life.

3.7.3 QALY Calculations

After the patient utilities and disutilities are calculated, the values are aggregated across the health states for each cycle to obtain the patient QALYs over time.

3.8 Cost Calculations

In the same manner that the health outcomes are calculated, the individual components of the cost outcomes are also calculated during each cycle. From the restricted societal perspective, these components include direct disease management costs by health state, drug acquisition, administration, monitoring, and dissociation (AE) management. Furthermore, the restricted societal perspective also includes patient time and transportation costs by health state. All costs are multiplied by the half-cycle-corrected patient counts.

Direct disease management costs are input by health state and based on whether patients have responded to treatment. The cost of the different health states differs between the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2), see section 5.5. At each cycle, the disposition of patients in each health state is multiplied by the management cost and summed across health states. The patients associated costs are calculated in a similar manner. The inputs are stratified by health state (i.e., MDE, response, remission, recovery).

The drug acquisition, administration and monitoring costs differ by treatment and disease phase (acute, maintenance). Furthermore, there are some differences between the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation, see section 5.5. However, in each cycle, the number of patients on treatment is multiplied by the appropriate drug acquisition, administration and monitoring costs for that cycle.

The derivation of the AE management cost is calculated similarly to the AE disutility. It is calculated for each AE as the product of the AE unit cost and the incidence of the event: $C_{AE} = C_{unit\ AE} \times I$, where:

- C_{AE} is the cyclic cost for a specific AE
- $C_{unit\ AE}$ is the cost of the AE
- I is the incidence of the AE per cycle length

This cost is calculated for all AEs and then summarised to give the AE-associated cost for each treatment per cycle. All costs mentioned above are summarised per model cycle to give the total direct cost for each cycle.

3.9 Time Horizon and Discounting

The base case assumptions are available in table 3. The time horizon for the economic analysis can be varied between 3, 5 and 7 years. An annual discount rate of 3.5%, as recommended by the Ministry of Finance, was applied to the costs and health benefits occurring beyond the first year. The time horizon for the base case is five years, as a shorter time horizon is not appropriate for TRD patients and it would not fully capture the health benefit of esketamine nasal spray plus oral AD. These assumptions are used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Table 3. Base case setting in the health economic analysis

Time	Discount rate cost	Discount rate health
5 years	3.5%	3.5%

3.9.1 Half-cycle Correction

Once the disposition of patients over time is calculated, a half-cycle correction is applied to ensure that outcomes are neither under- nor over-estimated. This is done by averaging the number of patients in each health state at the beginning and end of each cycle (35, 36). The half-cycle-corrected patient counts are used to calculate life years, QALYs, and costs. The half cycle correction is used for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

3.9.2 Discounting

All life years, QALYs, and costs are discounted by a user-specified discount rate (3.5% in the base case). At each cycle, outcomes are multiplied by the discount factor using the following formula: $\frac{1}{(1+r)^t}$, where r is the annual discount rate (for health or cost outcomes) and t is the time from time zero in years.

4 Data Sources: Treatment Efficacy

The transition probabilities assumed in the base case are shown in Table 4. Data sources and calculations are further described in the sections below. The transition probabilities are related to different phases of treatment, i.e. acute, optimization and maintenance. The duration of the acute phase is 4 weeks (TRANSFORM-2).(10) The maintenance phase is divided in two parts (SUSTAIN-1), first an optimization phase of 4 weeks and then a maintenance phase that starts after week 9.(11)

Table 4. Health State Transition Probabilities—Base case for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

Comparator	MDE to Remission*	MDE to Response*	Response to Remission†	Relapse†	Loss of Response†	Recurrence†
ESK + oral AD – full TRD population (clinical question 1)	0.525	0.168	0.199	0.056	0.042	0.029
Oral AD – full TRD population (clinical question 1)	0.310	0.210	0.124	0.123	0.149	0.029
ESK + oral AD – MSM ≥ 9 subpopulation (clinical question 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral AD – MSM ≥ 9 subpopulation (clinical question 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Evaluated at the end of the acute phase, †Per four-week cycle

4.1 Transition probabilities for Response and Remission (acute phase)

Transition from MDE to remission and response, for esketamine nasal spray plus oral AD data is derived from TRANSFORM-2. The observed cases approach was used to calculate response and remission. All remitters were assumed to also be responders; these patients were subtracted to get the transition probability of response without achieving remission. Data for the full population and the MSM ≥ 9 subpopulation is stated beneath, however the data for the MSM ≥ 7 and MSM ≥ 8 subpopulation are available in the excel model.

Full population (clinical question 1) transition probabilities in the acute phase:

- Remission (unadjusted) transition probability for the esketamine nasal spray plus oral AD arm: 0.525 = 53/101
- Response (unadjusted) transition probability for the esketamine nasal spray plus oral AD arm: 0.168 = (70-53)/101

MSM ≥ 9 population (clinical question 2) transition probabilities in the acute phase:

- Remission (unadjusted) transition probability for the esketamine nasal spray plus oral AD arm: [redacted]

- Response (unadjusted) transition probability for the esketamine nasal spray plus oral AD arm: [redacted]

Furthermore, the unadjusted estimates from TRANSFORM-2 gives the following transition rates for response and remission for 'Oral AD' in the base case analyses.

Full population (clinical question 1) transition probabilities in the acute phase:

- Remission transition probability for 'Oral AD': 0.310 = 31/100
- Response transition probability for 'Oral AD': 0.210 = (52-31)/100

MSM ≥ 9 population (clinical question 2) transition probabilities in the acute phase:

- Remission transition probability for 'Oral AD': [redacted]
- Response transition probability for 'Oral AD': [redacted]

The transition rates achieved in the comparator arm of the TRANSFORM-2 trial is based on the fact that patients have regular contact with healthcare professionals.

4.1.1 Alternative data sources for transition rates Response and Remission for the 'Oral AD' comparator arm

Treatment Resistant Depression in Stockholm (TRIST) RWE data cohort

Alternative transition rates for response and remission for the comparator arm were derived from the register-based Treatment Resistant Depression in Stockholm (TRIST) study, with a subset of patients with a clinical outcome measure recorded in the patient registers (initial analysis focused on MADRS-S).(37) This population was matched (using key baseline characteristics such as severity, previous AD failures and single/ recurrent episodes) to the placebo nasal spray population in TRANSFORM using the MAIC (matched-adjusted-indirect-comparison) methodology.

The transition probabilities for the 'Oral AD' comparator arm from this analysis are for both the full population (clinical question 1) and the MSM ≥ 9 subpopulation using TRIST:

- Response transition probability for the 'Oral AD' comparator arm: 0.107
- Remission transition probability for the 'Oral AD' comparator arm: 0.048

Furthermore, if TRIST data is used it will also be applied for the MSM ≥ 7 and MSM ≥ 8 subpopulations that are available in the excel model.

4.2 Transition probabilities for Response to Remission (maintenance phase)

Transition from response to remission for esketamine nasal spray plus oral AD, table 5, were derived from SUSTAIN-1, as it represents the best data source for the long-term effects of esketamine nasal spray plus oral AD. (11)

- Response to remission transition probability for the esketamine nasal spray plus oral AD arm for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2): 0.199

This analysis starts with patients who are "stable responders" at the beginning of the maintenance phase in SUSTAIN-1; these patients are followed over time to identify those who had a MADRS ≤12 for at least three of the last four weeks (three out of any four consecutive weeks during the follow-up). Any patient who successfully achieved this threshold is then counted as making the transition from response to remission, to estimate the rate (using Poisson regression analysis). The estimated transition rate from response to remission were assumed to be the same in both the full population and MSM ≥ 9 subpopulation.

Note that from the stable responders' group, those who had MADRS total score ≤12 at baseline as well as 2 more MADRS total score ≤12 during the first 3 post-baseline visits, satisfy the definition of remitters at baseline and are excluded from the analysis.

Table 5. Response to Remission Probabilities for the full TRD and MSM ≥ 9 population

Treatment	Mean (remission/ person days)	4 -week probability
ESK + oral AD	0.007937	0.199
Oral AD	-	0.124

The given rates are daily. Standard methodology was used to convert to 4-week probability. For example, the 4-week probability for esketamine nasal spray was calculated as: 1-EXP(-0.007937*365.25/(365.25/7)*4).

In the base case for the comparator arm, SUSTAIN-1 is used for response to remission transition rates.(11) However, as highlighted above in section 2.2.2, patients in SUSTAIN-1 have previously been treated successfully with esketamine nasal spray plus oral AD and thus there are some uncertainties related to the response to remission transition rate of the placebo nasal spray plus oral AD arm.

- Response to remission transition probability for the placebo nasal spray plus oral AD arm: 0.124

As for the esketamine + oral AD arm, the estimated transition rate from response to remission of 0.124 with were assumed to be the same in both the full population and MSM ≥ 9 subpopulation treated with the placebo nasal spray plus oral AD.

4.2.1 Alternative data sources for Response to Remission transition rates for the 'Oral AD' comparator arm

For the comparator arm, the STAR*D study can be used as an alternative source for response to remission transition rates, as it provides data on the durability of oral AD response and hence appropriate to inform the longer-term outcomes (9):

- Response to remission transition probability for oral AD: 0.032

More specifically the transition probability for response to remission for oral AD plus placebo treatment was based on Star*D trial Step 3 in sensitivity analyses (9). In the Star*D, 34.7% of patients reached remission at follow-up entry at.(9) The rate (4 weeks) for response to remission was 0.0327, which was converted to the 4-week pooled probability using the standard methodology: 1-EXP(-0.0327)=0.032. The same response to remission transition probability is assumed in the MSM ≥ 9 subpopulation, if STAR*D is used as alternative source. Furthermore, if STAR*D is chosen as alternative source it will also be applied to MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

4.3 Transition probabilities for Loss of Response (maintenance phase)

Loss of response is the transition from response to MDE and for esketamine nasal spray plus oral AD, data was derived from SUSTAIN-1 (11). The probabilities for esketamine nasal spray plus oral AD is available in table 6.

- Loss of response transition probability for the esketamine nasal spray plus oral AD arm in the full TRD population (clinical question 1) during maintenance phase: 0.042
- Loss of response transition probability for the esketamine nasal spray plus oral AD arm in the MSM ≥ 9 subpopulation (clinical question 2) during maintenance phase: [redacted]

Loss of response rate was based on those patients who were 'stable responders' at the beginning of the maintenance phase in SUSTAIN-1. All 'stable responders' who relapsed during the trial's full follow-up were counted for the calculation of the loss of response rates. The statistical analyses were based on counting the number of relapses over the total patient follow-up (in days), from the start of maintenance to a relapse event, or censoring. The mean rates (weekly) for loss of response for esketamine plus oral AD and oral AD plus placebo are 0.01071 and 0.04021, respectively. The standard methodology was used to convert the rates to 4-week probabilities; 0.042 (1-EXP(-0.01071*4)=0.042) for esketamine plus oral AD. Same methodology was applied to estimation of the loss of response transition probability of [redacted] for MSM ≥ 9 subpopulation (clinical question 2). The calculation to convert the weekly rates to the 4 week probabilities for the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

Table 6. Loss of Response Probabilities for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) treated with ESK + oral AD

Treatment	Mean Rate (weekly)	4 -week probability
ESK + oral AD - full TRD population	0.01071	0.042

Treatment	Mean Rate (weekly)	4 -week probability
(clinical question 1)		
ESK + oral AD - MSM ≥ 9 population (clinical question 2)	[redacted]	[redacted]

SUSTAINS-1 was used as the base case source for the loss of response transition rate for the 'Oral AD' comparator arm. However, as highlighted above there are some uncertainties in the results for the Oral AD comparator arm, since patients have previously been treated with esketamine nasal spray plus oral AD.

- Loss of response transition probability for the placebo nasal spray plus oral AD arm in the full TRD population (clinical question 1) during maintenance phase: 0.149
- Loss of response transition probability for the placebo nasal spray plus oral AD arm in the MSM ≥ 9 subpopulation (clinical question 2) during maintenance phase [redacted]

Loss of response rates are also derived based on those patients who were "stable responders" at the beginning of the maintenance phase in SUSTAIN-1 (11). All "stable responders" who relapsed during the trial´s full follow up were counted for the calculation of the loss of response rates. The statistical analyses were based on counting the number of relapses over the total patient follow-up (in days), from the start of maintenance to a relapse event, or censoring. The mean rates (weekly) for loss of response for oral AD plus placebo is 0.04021. The standard methodology was used to convert the rates to 4-week probability; 0.149 (1-EXP(-0.04021*4)=0.149) for oral AD plus placebo. Same methodology was applied to estimate the loss of response transition probability for the active comparator of [redacted] in the MSM ≥ 9 subpopulation. The calculation to convert the weekly rates to the 4 week probabilities for the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

4.3.1 Alternative data sources for Loss of Response transition rates for the 'Oral AD' comparator arm

The STAR*D data was again used as an alternative source for loss of response risk in the 'Oral AD' comparator arm.(9)

- Loss of response transition probability for the oral AD during maintenance phase for the full TRD population (clinical quesiton1) and the MSM ≥ 9 subpopulation (clinical question2): 0.224

Transition probabilities for loss of response for oral AD + placebo were also obtained from Star*D study based on the Step 3/4 (9). Kaplan-Meier (KM) plot for relapse during follow-up phase for participants who entered follow-up phase not in remission (but had adequately benefited from acute treatment) were digitized and an exponential distribution was fitted to the data using published methodology (38). The 4-week relapse risks for step three and four were estimated to be 22.2% and 22.8%. respectively (9). At baseline in SUSTAIN-1, 59% of the patients have had two treatment failures, while 41% of the patients have had three or more failures (Daly et al. 2019). This distribution of patients by previous treatment

failures was combined with the relapse risks from STAR*D (step three and step four), to calculate a weighted average loss of response risks for oral ADs (0.222*0.590+0.228*0.410=0.224) (9). The same response to remission transition probability as for the full population is assumed in the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations, if STAR*D is used as alternative source.

4.4 Transition probabilities for Relapse (maintenance phase)

Relapse is the transition from remission to MDE and for esketamine nasal spray plus oral AD data was derived from SUSTAIN-1 (11). The relapse rates associated with esketamine nasal spray plus oral AD are available in table 7.

- Relapse transition probability for the esketamine nasal spray plus oral AD arm for the full TRD population (clinical question 1) during maintenance phase: 0.056
- Relapse transition probability for the esketamine nasal spray plus oral AD arm for the MSM ≥ 9 subpopulation (clinical question 2) during maintenance phase: [redacted]

The relapse rate derived based on the assumption that patients reach the recovery health state after 36 continuous weeks (approximately 9 months) in remission. In particular, the relapse rate derived from those patients who are 'stable remitters' at the beginning of the maintenance phase in SUSTAIN-1 (11). All "stable remitters" who relapsed during the first 24 weeks of maintenance were counted for the calculation of the relapse rates. This timepoint was used because 24 weeks of maintenance + 12 weeks of optimization equals 36 weeks after the patient first reach remission. The analysis counts the number of relapses over the total patient follow up, from the start of maintenance to relapse or censoring over the first 24 weeks of maintenance. The mean relapse rate (weekly) for esketamine plus oral AD treatment was 0.01432 for the full TRD population (clinical question 1). Therefore, the 4-week probabilities using the standard methodology were 0.056 (1-EXP(-0.01432*4)=0.056) for esketamine plus oral AD. Same methodology was applied to estimation of the relapse rate of [redacted] for MSM ≥ 9 subpopulation (clinical question 2). The calculation to convert the weekly rates to the 4 week probabilities for the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

Table 7. Relapse Probabilities for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) treated with ESK + oral AD

Treatment	Mean Relapse Rate (weekly)	4 -week probability
ESK + oral AD – full TRD population	0.01432	0.056
ESK + oral AD - MSM ≥ 9 population	[redacted]	[redacted]

Standard methodology was used to convert to 4-week probabilities.

SUSTAIN-1 was also used as base case data source for the relapse transition rate for the 'Oral AD' comparator arm is SUSTAIN-1. However, as highlighted above there are some uncertainties in the results for the Oral AD comparator arm, since patients have previously been treated with esketamine nasal spray plus oral AD.

- Relapse transition probability for the placebo nasal spray plus oral AD arm for the full TRD population (clinical question 1) during maintenance phase: 0.123
- Relapse transition probability for the placebo nasal spray plus oral AD arm for the MSM ≥ 9 subpopulation (clinical question 2) during maintenance phase: [redacted]

Relapse rates for the placebo nasal spray plus oral AD arm are derived based on the same methodology as described above. The mean relapse rate (weekly) for oral AD plus placebo treatment was 0.03284 for the full TRD population (clinical question 1). Therefore, the 4-week probabilities using the standard methodology was 0.123 (1-EXP(-0.03284*4)=0.123) for oral AD plus placebo treatment. Same methodology was applied to estimation of the relapse rate of [redacted] for MSM ≥ 9 subpopulation (clinical question 2). The calculation to convert the weekly rates to the 4 week probabilities for the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

4.4.1 Alternative data sources for Relapse transition rates

The STAR*D trial was again used as an alternative source for the relapse rates for the 'Oral AD' comparator arm (9). Using the same methodology as described above (for loss of response) but applied to the Kaplan-Meier plot for relapse during follow-up phase for participants who entered follow-up phase in remission, 4-week relapse risks for Step 3 and 4 were estimated to be 6.8% and 12.8%, respectively. Using the SUSTAIN-1 distributions of two (59%) and three or more (41%) failures, a weighted average relapse risk for oral AD was estimated to be 9.2%. (0.0677*0.5900+0.1279*0.4100=0.0924).

- Relapse transition probability for the oral AD during maintenance phase for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2): 0.092

The same relapse transition probability as for the full population is assumed in the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations, if STAR*D is used as alternative source.

4.5 Transition probabilities for Recurrence (maintenance phase)

Recurrence is the transition from recovery to MDE and indicates a new depressive episode, were the pooled rate from SUSTAIN-1 (after 36 weeks, approximately 9 months of relapse-free remission) was applied to both treatment arms. Recurrence rates for the full TRD population is available in table 8.

- Pooled relapse transition probability during recurrence phase for the full TRD population (clinical question 1): 0.029
- Pooled relapse transition probability during recurrence phase for the MSM ≥ 9 subpopulation (clinical question 2): [redacted]

Recurrence (i.e. the transition from recovery to MDE) rates were derived from those patients who are 'stable remitters' at the beginning of the maintenance phase (SUSTAIN-1) (11). All 'stable remitters' who relapsed after 24 weeks of maintenance treatment (equal 36 weeks post-acute treatment) were counted for the calculation of the recurrence rates. The analysis counted the number of relapses over the total patient follow up, from week 25 to relapse or censoring. For the full TRD population (clinical question 1) the mean relapse rates (weekly) for esketamine plus oral AD and oral AD plus placebo were 0.006142 and 0.009056, respectively. The pooled relapse rate (weekly) was 0.0073, which was conservative for esketamine. The pooled relapse rate (weekly) was converted to the 4-week pooled probability using the standard methodology: 1-EXP(-0.0073*4)=0.029, and was applied to the full TRD population (clinical question 1). The pooled data is the relapse rates observed in SUSTAIN-1 for both treatment arms, i.e. assuming that the recurrence rate after the 24- week maintenance treatment was the same between the treatment arms. This a conservative assumption as no additional clinical benefit was assumed for esketamine nasal spray plus oral AD compared to oral AD in the recovery health state.

The same methodology was applied to estimate the pooled relapse transition probability of [redacted] for MSM ≥ 9 subpopulation. The pooled 4 week probabilities for the MSM ≥ 9 subpopulation as well as the MSM ≥ 7 and MSM ≥ 8 subpopulations are available in the excel model.

Table 8. Recurrence Probabilities from SUSTAIN-1 for full population (clinical question 1)

Treatment	Mean Relapse Rate (weekly)	4 -week probability
Esketamine nasal spray plus oral AD – full TRD population (clinical question 1)	0.006142	
Placebo nasal spray plus oral AD – full TRD population (clinical question 1)	0.009056	
Pooled – full TRD population (clinical question 1)	0.0073	0.029

Standard methodology was used to convert to 4-week probabilities.

For patients on esketamine nasal spray plus oral AD, the risk of recurrence stays the same after stopping treatment with esketamine as they continue on oral AD for recurrence prevention.

4.5.1 Subsequent treatment

For subsequent treatment, the model includes up to five treatment options for which their market share can be defined. The model uses the market shares to calculate weighted average inputs for the transitions during the subsequent treatment phase. Currently it is assumed that all patients receive the same treatment mix, which consists of a mix of oral ADs.

Table 9 shows the efficacy estimates for the oral ADs defined in the subsequent treatment of both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation. Efficacy for the oral ADs used as subsequent treatment were sourced from Edwards et al 2021 (39), which is a meta-analysis reviewing depression treatments such as lithium and antipsychotics. This is an appropriate source for the efficacy rate in this population, as these treatments are recommended in Danish guidelines and used in clinical practice. The health state transition probabilities for the subsequent treatment mix, stated in table 9, is assumed to be the same for both the full TRD population and the MSM ≥ 9 subpopulation.

Risks from this source for response discontinue, remission discontinue, relapse from response discontinue, relapse from remission discontinue were used to inform response, remission, loss of response, and relapse for this model, respectively. Standard methodology was used to convert 2-month risks to 4-week risks.

Table 9. Health State Transition Probabilities—Subsequent Treatment mix

Treatment	Response†*	Remission†	Loss of Response†	Relapse†
Subsequent treatment mix of Oral ADs	0.008	0.004	0.104	0.042

†Per four-week cycle

*Response minus remission

5 Data Sources: Other

5.1 Treatment Discontinuation

The risk of discontinuation per cycle for the base case treatments are shown in Table 10. The same risk of discontinuation per cycle was applied for the full TRD population and the MSM ≥ 9 subpopulation.

Table 10. Discontinuation Risk—Base case treatments

Comparator	Acute		Maintenance Week 5-8		Maintenance in Response/Remission		Recovery	
	Risk	SE	Risk	SE	Risk	SE	Risk*	SE
ESK + oral AD	0.000	0.000	0.017	0.004	0.017	0.004	0.249	0.062
Oral AD	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

*Based on assumptions

The following assumptions were used for the discontinuation rates

- Acute phase: no discontinuation was allowed for any of the treatment arms
    - After the acute phase (4 weeks of treatment), it is assumed that 30% of the patients in the full TRD population discontinue esketamine nasal spray due to non-response, whereas [redacted] of the MSM ≥ 9 subpopulation discontinue (TRANSFORM-2).

- Maintenance phase:
    - Discontinuation for any reason: an exponential distribution was fitted to pooled data from SUSTAIN-1 of stable responders and stable remitter on discontinuation for any reason with relapse as censoring events.(11) The estimated 4-week risk was 1.69% (20% annually) (40). The discontinuation risk of 1.69% per cycle was applied for the full TRD population and the MSM ≥ 9 subpopulation.
    - Discontinuation due to recovery: in the base case it was assumed that 70% of the patients discontinue esketamine nasal spray at recovery (after 36 weeks of treatment). This assumption was applied for the full TRD population and the MSM ≥ 9 subpopulation.
        - It is not possible in the model to have different stopping rules within the same health state, the base case reflects the assumption that the majority of patients will stop after 6-12 months of esketamine nasal spray treatment.
            - The proportion (70% in the base case) of the patients discontinuing discontinue esketamine nasal spray at recovery (after 36 weeks of treatment), can be varied for purposes of sensitivity analyses. The proportion can be adjusted under the sheet "Clinical inputs" cell "E55"
        - The remaining patients gradually discontinue esketamine, where 99% stops after 2 years of maintenance treatment (24.9% per cycle). SE was assumed to be 25%

of the mean value. This assumption was applied for the full TRD population and the MSM ≥ 9 subpopulation.

- The remaining patients who gradually discontinue esketamine, can be varied for purposes of sensitivity analyses. The proportion which stops after 2 years of maintenance treatment can be adjusted under the sheet "Clinical inputs" cell "E71"

All patients who discontinue esketamine nasal spray remains on oral AD until they experience a recurrence or death.

5.2 Adverse Events

The model includes AEs that were experienced by ≥5% of subjects in any of the treatment groups of the TRANSFORM-2 trial (Popova et al 2019). The model requires four types of inputs related to AEs: (1) four-week incidence, (2) unit cost, (3) disutility, and (4) duration.

5.2.1 Adverse Event Incidence

The four-week incidences of AEs for the treatments are shown in table 11 and was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) as there are no stratified data for the subpopulation. Treatment-related AEs are assumed to occur only during the acute phase of treatment. They are not considered in the maintenance phase as it is assumed that patients will have adjusted well to treatment and would not have a negative impact on the utility. The inclusion of a visit due to adverse events as a result of esketamine nasal spray administration is conservative, as clinical data shows that the majority of the adverse events occur at the time of nasal spray administration, hence the need for observation by a healthcare professional.

Table 11. Four-week Incidence of AEs - Acute phase for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

AE	ESK + oral AD	Oral AD
Anxiety	0.104	0.046
Blood pressure increased	0.096	0.000
Delusional perception	0.052	0.000
Derealization	0.078	0.018
Diarrhea	0.087	0.092
Dissociation	0.122	0.018
Dizziness	0.209	0.046
Dizziness postural	0.070	0.009
Dry mouth	0.078	0.028
Dysgeusia	0.243	0.119
Fatigue	0.043	0.055
Feeling abnormal	0.087	0.009
Feeling drunk	0.070	0.009

AE	ESK + oral AD	Oral AD
Headache	0.183	0.174
Hypoesthesia	0.070	0.009
Hypoesthesia oral	0.078	0.009
Illusion	0.052	0.009
Insomnia	0.096	0.055
Nasal discomfort	0.070	0.018
Nausea	0.261	0.064
Paranesthesia	0.113	0.009
Paranesthesia oral	0.078	0.009
Somnolence	0.130	0.064
Throat irritation	0.078	0.046
Vertigo	0.261	0.028
Vision blurred	0.122	0.028
Vomiting	0.096	0.018

5.2.2 AE Disutilities and Duration

The duration and disutility of each AE is shown Table 12 and was applied for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) as there are no stratified data for the subpopulation. The disutility due to dry mouth was obtained from a study by Revicki et al 1998 (41). The study reported the utilities for patients with MDD who had completed at least eight weeks of treatment in North America. The disutility due to vision blurred was from Sullivan et al. 2006, which reported European Quality of Life, five dimensions (EQ-5D) index scores for chronic conditions in the US, estimated from the nationally representative Medical Expenditure Panel Survey pooled from 2000–2002 with 38,678 adults (42). Other disutilities listed in Table 12 were from the study by Sullivan et al. 2004, a cost-effectiveness study of eight ADs used as initial treatment for depression in the US.(43) AEs observed in TRANSFORM-2 were transient and were resolved within hours (10). Therefore, all AEs were assumed to last for one day.

Table 12. AE Disutilities and Duration for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

AE	Disutility			Duration	Source
	Value	SE	Source		
Anxiety	-0.129	0.03225	Sullivan et al., 2004	0.14 weeks	Assumption
Blood pressure increased					
Delusional perception					
Derealization					
Diarrhea	-0.044	0.011	Sullivan et al., 2004	0.14 weeks	Assumption
Dissociation					

AE	Disutility			Duration	Source
	Value	SE	Source		
Dizziness	-0.085	0.02125	Sullivan et al., 2004*	0.14 weeks	Assumption
Dizziness postural					
Dry mouth	-0.010	0.0025	Revicki et al., 1998		
Dysgeusia					
Fatigue	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Feeling abnormal	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Feeling drunk	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Headache	-0.115	0.02875	Sullivan et al., 2004	0.14 weeks	Assumption
Hypoesthesia					
Hypoesthesia oral					
Illusion	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Insomnia	-0.129	0.03225	Sullivan et al., 2004	0.14 weeks	Assumption
Nasal discomfort					
Nausea	-0.065	0.01625	Sullivan et al., 2004	0.14 weeks	Assumption
Paranesthesia					
Paranesthesia oral					
Somnolence	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Throat irritation	-0.010	0.0025	Assumption‡		
Vertigo	-0.085	0.02125	Assumption†	0.14 weeks	Assumption
Vision blurred	-0.050	0.01245	Sullivan et al., 2006	0.14 weeks	Assumption
Vomiting	-0.065	0.01625	Assumption§	0.14 weeks	Assumption

*Assumed to be the same as for drowsiness in Sullivan et al. 2004.

† Assumed to be the same as for dizziness.

‡Assumed to be the same as for dry mouth.

§Assumed to be the same as nausea.

5.3 Quality of Life

The health state utilities based on EQ-5D-5L for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) are shown in Table 13. Utilities associated with the health states were obtained from TRANSFORM-2 patient-level data, using DK weights published by Jensen et al (2021).(10) (34)

More specifically, the TRANSFORM-2 trial provides each patient's response to the EQ-5D-5L health state questionnaire, which consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five levels for each dimension (no problems, slight problems, moderate problems, severe problems, and extreme problems). The responses for the dimensions and levels are combined to produce a five-digit number to describe a patient's health state (ranging from 11111 to 55555). In order to quantitatively analyze EQ-5D data, a mapping must be done for each patient's five-digit EQ-5D-5L questionnaire response to a utility index value representing societal preference weights or

utilities. Each country-specific mapping, informed by societal preferences, is called a value set and contains values that range from less than 0 (a value of 0 is equivalent to death, negative values represent a health status worse than death) and up to 1 (a 1 is equivalent to a perfect health state). For Denmark, Jensen et al published an article on the derivation of a direct EQ-5D-5L value set. The health states utility value in this health economic analysis reflect the use of the direct EQ-5D-5L value set developed by Jensen et al. 2021.

Table 13. Health State Utilities for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

Health State	Utility	SE	Utility	SE	Source
Population	Full TRD (clinical question 1)		MSM ≥ 9		
MDE	0.382	0.0156	[redacted]	[redacted]	TRANSFORM-2
Response	0.827	0.0200	[redacted]	[redacted]	TRANSFORM-2
Remission	0.921	0.0130	[redacted]	[redacted]	TRANSFORM-2
Recovery	0.921	0.0130	[redacted]	[redacted]	Assumption*

*Assumed to be the same as remission

5.4 Mortality

Age- and gender-specific all-cause mortality risks for the general population were obtained from Statistics Denmark. The all-cause risk data for the general population is available in the excel model and reflects most recent evidence from Statistics Denmark, reflecting 2020. Suicide-related mortality risk is presented in Table 14 and is sourced from Bergfeld et al 2018. (33) The all cause and suicide-related mortality risk was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Table 14. Suicide-related Mortality Risk for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

Health State	Annual Rate of Completed Suicide	SE	Source
MDE	0.0047	0.00118	Bergfeld et al. 2018
Response	0.00235	0.00059	Assumption*
Remission	0.0	0.0	—
Recovery	0.0	0.0	—

* Assumed to be half of the rate for the MDE health state

5.5 Resource use and costs

5.5.1 Disease Management

To estimate the direct medical care costs associated with the different health states of the model i.e. MDE, response, remission and recovery, RWE evidence on the healthcare utilization of SSRI and SNRI used to treat TRD patients in Denmark was used. The RWE derives from the study, TRIDEN: Treatment Resistant Depression in Denmark. The costs of the different health states for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) are summarized in Table 15.

Table 15. Direct Medical Care Costs for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

Health State	Medical Care Costs (per 28-day cycle)	SE	Medical Care Costs (per 28-day cycle)	SE
Population	Full TRD (clinical question 1)		MSM ≥ 9	
MDE	DKK 4.582	DKK 1.146	DKK 5.654	DKK 1.414
Response	DKK 2.614	DKK 654	DKK 3.226	DKK 806
Remission	DKK 646	DKK 162	DKK 797	DKK 199
Recovery*	DKK 646	DKK 162	DKK 797	DKK 199

* Assumed to be the same as remission

The study was conduct by an external research group at Bispebjerg and Frederiksberg Hospital and sponsored by Janssen. The external research group extracted and analyzed the data from Danish registries, thus the results are unbiased and provides new essential scientific information on the treatment of TRD patients in Denmark. Furthermore, some of the researchers have formerly published RWE data on TRD patients in Denmark (4). This underlines the validity of the conducted analyses and that the external research group´s competence. In addition, the TRIDEN results are planned to be published in scientific journals, thus the results will eventually be public. Furthermore, we use this data with reference to the Medicine Council´s guide on methodology for cost-analysis of new drugs and indications in the hospital sector, which states that the source of the cost information can be studies, expert reviews or a mix. (22)

The purpose of the study was to describe the treatment patterns of TRD patients and analyze the healthcare utilization of TRD patients in Denmark, using a nationwide cohort.

All information on health care utilization at the hospital were derived from Danish National Patient Registry (DNPR) and the analysis was done using data from 1996 to 2016. Data from general and specialist was from the National Health Insurance Service System. Only completed contacts were studied in DNPR. For contacts to GP, private psychiatrist, private psychologist, and other private primary health care specialists, only contacts where the patient and health care specialist have met are accounted (e.g. phone calls and emails are not accounted). Furthermore, all information on depression severity were derived from Danish National Patient Registry (DNPR). Data from refills of prescriptions for antidepressants were identified in the Danish National Prescription Registry using the ATC-code N06AB for SSRI and ATC-code N06AX for SNRI.

5.5.1.1 Calculation of disease management cost of the MDE health state for the full TRD population (clinical question 1)

TRIDEN reported average healthcare utilization in the first year after TRD, given for patients treated with SSRI or SNRI as first line treatment. The reported utilization was used to calculate the disease management cost associated with the different health states of the model. The reported utilization is the best available estimate to calculate the yearly costs associated a depressive episode amongst TRD patients. An overview of the average healthcare utilization by TRD patients treated with SSRI or SNRI in the first year after TRD is available in Table 16 beneath and applied to calculate the MDE health state cost for the full TRD population (clinical question 1). It is worth noticing that the reported healthcare utilization in table 16, deriving from TRIDEN, is for a TRD population consisting of both mild, moderate and severe patients. Consequently, it is a conservative estimate as a patient population with a mild depressive episode would have a lower cost than a population only including patients with a moderate to severe depressive episode. Furthermore, it is worth noticing that the reported healthcare utilization in Table 16 is not exclusively for patients with MDE. Instead the healthcare utilization is reported for a patient population which might include patients with both MDE, response and remission. Consequently, the healthcare utilization for the MDE health state might be underestimated as an patient population exclusively consisting of MDE patients would have a higher cost than a population including more well treated i.e. responders and remitters.

The healthcare utilization used to calculate the cost associated with a health state MDE was acute hospitalization days, elective hospitalization days and emergency department visits within psychiatry. The TRIDEN study also reported outpatient visits and home visits, however that specific utilization was deemed to be associated with the treatment of SSRI and SNRI and therefore excluded in the calculation of the MDE health state cost. Furthermore, the exclusion is due to the fact that an inclusion of the reported outpatient and home visits in the calculation of the cost for the health states would create a double counting for the Spravato patients as the outpatient visits are accounted for in the administration cost. However, an additional follow-up outpatient visit each month is assumed for patients treated with Spravato but this utilization is applied under administrations cost. This is to account for a doctor's consultation that is not associated with the actual administration of esketamine nasal spray. For the actual cost estimation, see section 5.5.2.3 on page 40.

Somatic healthcare utilization was also used to calculate the cost associated with the MDE health state. Somatic healthcare utilization is important to include as there has been observed an increased risk of developing comorbidities, for patient with TRD. In this case the outpatient visits were included as they were deemed to occur due to the increased risk of comorbidities amongst TRD patients and not entirely due to specific anti-depressive treatment. Lastly, GP visits were also included in the calculation of the cost associated with the MDE health state.

Table 16: Average healthcare utilization in the first year after TRD for patients treated with SSRI or SNRI as first line antidepressant treatment after TRD.

Type of health care utilization	*SSRI Mean (SD)*	*SNRI Mean (SD)*
Psychiatric contacts		
Acute hosp. days	4.7 (19.7)	5.3 (20.4)

Type of health care utilization	*SSRI Mean (SD)*	*SNRI Mean (SD)*
Elective hosp. days	1.0 (8.5)	1.1 (10.5)
ED visits	0.2 (0.9)	0.2 (1.3)
Somatic contacts		
Acute hosp. days	2.6 (8.8)	2.0 (8.2)
Elective hosp. days	0.7 (4.0)	0.6 (4.4)
ED visits	0.4 (1.1)	0.3 (0.9)
Outpatient visits	3.2 (7.3)	3.0 (7.0)
GP	9.2 (9.5)	9.6 (9.4)

The reported healthcare utilization was multiplied with associated DRG-2021 tariffs and tariffs from the Medicine Council´s valuation of unit cost to estimate the disease management cost associated with the MDE health state for full TRD population (clinical question 1).(44)

The cost associated with the different types of healthcare utilization (hospital days, ED visits, outpatient visit) were calculated using DRG-2021 tariffs, see Table 17. The specific DRG-2021 tariffs for psychiatric healthcare utilization was identified using the reported "psykiatritakster 2021" by Sundhedsdatastyrelsen. Furthermore, the specific DRG-2021 tariffs for the different somatic healthcare utilizations was identified using the interactive DRG system by Sundhedsdatastyrelsen.

Table 17. DRG-2021 tariffs and the Medicine Council´s valuation of unit cost used to calculate cost of health care utilization.

Type of healthcare utilization	DRG code	Group name	Price (DKK)
Psychiatric outpatient visit	n/a	AMBULANT	1.944
Somatic outpatient visit	19MA98	MDC19 1-dagsgruppe, pat. mindst 7 år	2.116
Psychiatric emergency room visit	n/a	AMBULANT	1.944
Somatic emergency room visit	19MA98	MDC19 1-dagsgruppe, pat. mindst 7 år	2.116
Acute/elective somatic hospitalization day	19MA02	Depressive neuroser	16.487
Acute/elective somatic hospitalization day "langliggertakst" applied after 4 days	19MA02	Depressive neuroser	2.127
Acute/elective psychiatric hospitalization day	n/a	SENGEDAGE	3.885
Somatic home visit (assumption)	19MA98	MDC19 1-dagsgruppe, pat. mindst 7 år	2.116
Psychiatric home visit (assumption)	n/a	AMBULANT	1.944
Consultation (GP)	n/a	Ydelser i almen praksis	147

The average yearly cost as well as the 4 week cost associated with the MDE health state for the full TRD population (clinical question 1) is available in table 18. The table shows the yearly MDE health state cost is 59.777 DKK, which derived assuming an even distribution of the cost associated with SSRI and SNRI. The 4-week cost associated with the MDE health state, which is applied in the model base case for the full

TRD population (clinical question 1), was calculation using following equation; 59.777/365,25*7*4= 4.582.

Table 18: The yearly and 4-week average disease management cost associated with the MDE health state for the full TRD population (clinical question 1).

Type of health care utilization	MDE health state cost (DKK)
Psychiatric contacts	
Acute hosp. days	19.425
Elective hosp. days	4.079
ED visits	389
Somatic contacts*	
Acute hosp. days	16.487
Elective hosp. days	10.717
ED visits	741
Outpatient visits	6.560
GP	1.380
Total yearly cost	59.777
Total 4 week cost	**4.582**

*It is worth noticing that the cost applied for somatic acute hospitalization days equals the DRG-2021 tariff of 16.487. This is since the number of hospitalization days is less than 4 and consequently the "langliggertakst" will not be applied. The calculation can be found in the sheet "Health state calc" in the excel model.

The disease management cost estimation assumptions and approach presented in the paragraphs above was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

5.5.1.2 Calculation of disease management cost of the MDE health state for the MSM ≥ 9 subpopulation (clinical question 2)

The TRIDEN report was also utilized to estimate the MDE health state cost for the MSM ≥ 9 subpopulation. However, as the MSM ≥ 9 subpopulation is a more severe TRD population, with e.g. [redacted] of the MSM ≥ 9 patient in TRANSFROM-2 having a severe depressive episode, the cost described above based on the average healthcare utilization in the first year after TRD, given for patients a having mild, moderate or severe depressive episode does not provide an adequate estimation. Instead average healthcare expenses given for a patient population having a severe depressive episode and who received SSRI and SNRI as first line treatment of antidepressant after TRD diagnosis is used, see table 19. The yearly cost associated with SSRI and SNRI as first line treatment of TRD for patient with a severe depressive episode was, by the external research group at Bispebjerg and Frederiksberg Hospital,

reported to 73.758 DKK. The 4-week cost associated with the MDE health state, which is applied in the model base case for the MSM ≥ 9 subpopulation (clinical question 2), was calculated using following equation; 73.758/365,25*7*4= 5.654 DKK.

Table 19: The yearly and 4-week average disease management cost associated with the MDE health state for the MSM ≥ 9 subpopulation (clinical question 2).

Type of health care utilization	MDE health state cost (DKK)
Psychiatric contacts	57.529
Somatic contacts*	15.129
GP	1.100
Total yearly cost	73.758
Total 4 week cost	5.654

This is still a quite conservative estimate as e.g. [redacted] of the MSM ≥ 9 population in TRANSFORM-2 has failed on 3-4 AD treatments and not only 2. It can reasonably be assumed that there is a higher cost associated with patients having failed 3-4 AD treatments and having a severe depressive episode than a population consisting of patient with a severe depressive episode having failed 2 AD treatment.

However, the estimated 4-week cost of 4.582 DKK associated with the MDE health state for the full TRD population (clinical question 1) and the cost of 5.654 DKK for the MSM ≥ 9 subpopulation (clinical question 2) fits well with the results of from Swedish study on the societal cost of depression (45). The Swedish study was a retrospective database study using data from 10.430 adult patients with depression in psychiatric care between 2006 and 2008. Data came from registries in the Stockholm region and national Swedish registries. This study reported yearly costs stratified by depressive episode and remission, corresponding to two health states in the model.

The study found that the mean annual costs of depression was € 17.279 in 2008. 88% of the costs were due to productivity loss, followed by 6% in outpatient costs, 4,3% inpatient costs and 1,5% related to pharmaceuticals. Costs during a depressive episode were € 7.042 per month in 2008. Corresponding to this, patients had a cost of € 993 per month while in remission. Using the distribution of costs mentioned above, 10.3% of these monthly costs are linked to inpatient and outpatient care. Hence, indirect costs linked to production loss and costs of pharmaceuticals, is excluded when calculating direct medical costs. The monthly costs during a depressive episode of € 7.042 in 2008 which is adjusted to only account for direct medical costs only (10,3 %) results in € 725. That amount corresponds well with the estimated cost of 4.582 DKK and 5.654 DKK per 4 week cycle, for the full TRD population (clinical question 1) and MSM ≥ 9 subpopulation (clinical question 2), respectively.

5.5.1.3 Calculation of disease management cost for the remission, response and recovery health states

The rate between the costs during a depressive episode of € 7.042 per month and the cost of € 993 per month while in remission, as reported by Ekman et al 2013 and described above, was used to calculate disease management cost associated with the remission health state.(45) The rate was calculated dividing 7.042 with 993 resulting in a rate of 7.09. This rate was then used to calculate the cost associated with the remission health state by dividing the MDE health state cost per 4 week cycle of 4.582 DKK for the full TRD population (clinical question 1) and 5.654 DKK for MSM ≥ 9 subpopulation (clinical question 2) with 7.09. Consequently, the cost associated with the remission health state is 646 DKK and 797 DKK (table 20) per 4 week cycle for the full TRD population (clinical question 1) and MSM ≥ 9 subpopulation (clinical question 2), respectively. Furthermore cost for response were assumed to be an average of MDE and resmission, and costs in recovery were assumed to be the same as remission. Consequently, for the full TRD population (clinical question 1), the cost associated with the response health state is 2.614 DKK per 4 week cycle and the cost associated with the recovery health state is 646 DKK per 4 week cycle, see table 20. For the MSM ≥ 9 subpopulation (clinical question 2), the cost associated with the response health state is 3.226 DKK per 4 week cycle and the cost associated with the recovery health state is 797 DKK per 4 week cycle.

Table 20: The cost associated with the MDE, remission, response and recovery health states for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Health states	Cost (DKK)	
	Full TRD population (clinical question 1)	MSM ≥ 9 subpopulation (clinical question 2)
MDE	4.582	5.654
Response	2.614	3.226
Remission	646	797
Recovery	646	797

The disease management cost estimation assumptions and approach presented in the paragraphs above was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

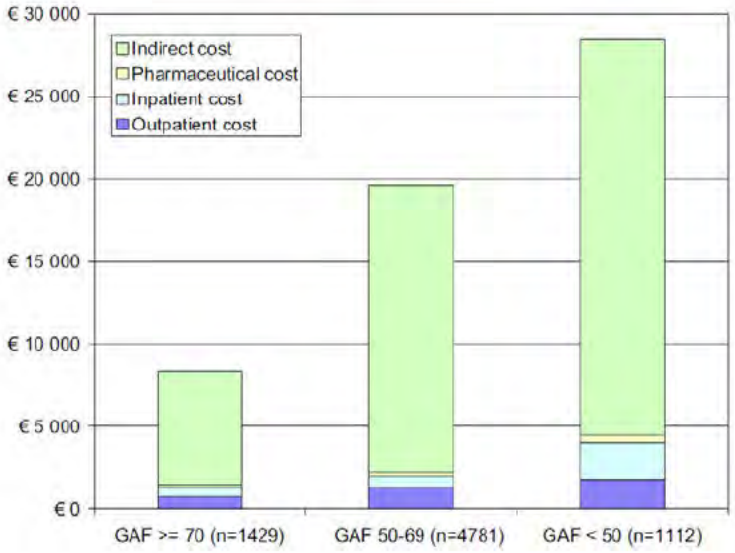
5.5.1.4 Indirect cost

According to the Medicine Council´s guidelines, the inclusion of production loss is generally not accepted. However, since depression and TRD have a significant impact on society, it can be argued that the societal perspective is highly relevant and should therefore be included as a scenario.

Indirect costs are calculated by incorporating the productivity loss due to sick leave or early retirement for patients. Work hour loss per week for patients is shown in Table 21 and are based on the same Swedish study as the direct medical costs. In the Swedish study, yearly costs were stratified by disease severity defined by Global Assessment of Functioning classes (GAF).(45) For the model, it was assumed

that the cost for patients (GAF) < 50 was representative for the MDE health state, GAF 50-69 was representative for the response health state, and GAF ≥ 70 was deemed representative for remission and recovery. Details on how indirect costs due to sick leave and early retirement are calculated is below.

Figure 3: Cost distribution in depression by severity



As shown in Figure 3 above, the reported total cost per year with severe depression (GAF < 50) was €28.472. Correspondingly, Ekman et al. estimated the total cost per year for patients with moderate depression (GAF 50-69), to be approximately €19.900 and reported yearly costs of mild depression (GAF ≥ 70) to be €8.306. As illustrated in Figure 3 above, the majority of costs, 88,2% on average, stem from indirect costs due to production loss from sick leave or early retirement.
Using this distribution, we find that for severe depression (GAF < 50) the total annual indirect costs were €25.112. The corresponding annual indirect costs for patients with moderate depression (GAF 50-69) are €17.551 and €7.326 for mildly depressive patients (GAF ≥ 70). (45)

When calculating indirect costs, Ekman et al. used a cost estimate of €26 per hours lost in 2008. Dividing total indirect costs by the cost per hour, we find that patients in a severe depressive state lose 966 productive hours annually due to sick leave and early retirement. Moderately depressed patients lose 675 hours annually and patients with mild depression lose 282 hours. This is the equivalent of losing 18.6, 13 and 5.4 productive hours per week for severe, moderate and mild depression respectively. As stated previously, for the model, it was assumed that the productive hours lost for patients in the severe state (GAF < 50) was representative of the MDE state, the moderate state (GAF 50-69) was representative of the response state and finally the mild state (GAF ≥ 70) was representative of response and recovery state. (45)

As an estimate of how the Danish society value production, the average hourly salary of 323,52 DKK including tax is used, see table 21. This hourly salary was obtained through "Danmarks Statistik LONS20: Løn efter arbejdsfunktion, sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn".

Table 21. Indirect Costs: Patients

Category	Mean	SE
Hourly wage	DKK 323,52	DKK 80,88
Absenteeism (work hours loss per week)		
MDE	18.57	4.64
Response	12.98	3.25
Remission	5.42	1.36
Recovery	5.42	1.36

The aggregated indirect costs per cycle and health state are shown in Table 22 and applied for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Table 22. Aggregated Indirect Costs per 4-week Cycle

Health State	Work Productivity Loss
MDE	DKK 24.031,07
Remission	DKK 16.797,16
Response	DKK 7.013,91
Recovery	DKK 7.013,91

In addition, the model can include a one-time cost for treatment failure. This represents acute costs associated with high resource utilization right after treatment failure (e.g., loss of response, relapse, recurrence, or not response). In the base case, this parameter was not used, as it is a more conservative approach but has a small impact on the overall costs.

5.5.2 Drug Acquisition and Administration and Monitoring Costs

The number of session and dosage required by each treatment i.e. esketamine and OAD and disease phase is stated in Table 23. In addition, number of session and dosage required associated with esketamine treatment is stated separately for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). It is assumed that the dosing of OAD does not differ between the two populations.

The drug acquisition cost is available in Table 24 whereas administration and monitoring and patient costs per cycle for each treatment and populations are shown in Table 25.

Table 23. Average Number of Sessions per Week and Dosage

Esketamine (Flexible Dose)	Market Share	Acute		Maintenance weeks 5-8		Maintenance weeks 9-40		Recovery	
		Number of Sessions	Number of Devices	Number of Sessions	Number of Devices	Number of Sessions	Number of Devices	Number of Sessions	Number of Devices

Esketamine – full TRD population (clinical question 1)	—	1.850	2.530	0.992	2.605	0.711	2.605	0.675	2.571
Esketamine – MSM ≥ 9 subpopulation (clinical question 2)	-	1.917	2.642	1.000	2.720	0.725	2.720	0.619	2.667
Oral AD	Market Share	Number of doses	Dosage	Number of Sessions	Dosage	Number of Sessions	Dosage	Number of Sessions	Dosage
Duloxetine	25%	7	120 mg	7	120 mg	7	120 mg	7	120 mg
Escitalopram	25%	7	20 mg	7	20 mg	7	20 mg	7	20 mg
Sertraline	25%	7	200 mg	7	200 mg	7	200 mg	7	200 mg
Venlafaxine	25%	7	375 mg	7	375 mg	7	375 mg	7	375 mg

Table 24. Drug Acquisition Cost per 4-week Cycle

Treatment	Acute	Continuation	Maintenance	Recovery
ESK + oral AD – full TRD population (clinical question 1)	DKK 26.804,50	DKK 14.823,47	DKK 10.648,47	DKK 9.969,96
ESK + oral AD – MSM ≥ 9 subpopulation (clinical question 2)	DKK 28.995,13	DKK 15.601,06	DKK 11.321,09	DKK 9.494,67
Oral AD	DKK 56.48	DKK 56.48	DKK 56.48	DKK 56.48
Subsequent Treatment Mix	Acute		Maintenance	
Subsequent Treatment Mix	DKK 56.48		DKK 56.48	

Table 25. Total Administration, Monitoring and Patient cost per 4-week Cycle

Treatment	Acute	Continuation	Maintenance	Recovery
ESK + oral AD – full TRD population (clinical question 1)	DKK 7.142,62	DKK 3.829,01	DKK 3.136,48*	DKK 2.994,41*
ESK + oral AD – MSM ≥ 9 subpopulation (clinical question 2)	DKK 7.399,61	DKK 3.860,67	DKK 3.187,69*	DKK 2.780,96*
Oral AD	DKK 4.788	DKK 4.788	DKK 4.788	DKK 4.788
Subsequent treatment Mix	Acute		Maintenance	
Subsequent Treatment Mix	DKK 4.804,55		DKK 4.804,55	

*including one additional follow-up visit per month

The drug acquisition and administration/monitoring cost estimation assumptions and approach presented in the tables above and following sections was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

5.5.2.1 Drug acquisition Spravato

The average unit cost per 28mg device of esketamine nasal spray is DKK 1.428,73 which was calculated based on the pooled average of the current AIP of the three different packages of esketamine nasal spray available, see table 26. The number of administrations for esketamine nasal spray were estimated using the average number of sessions per week and devices per session in the induction phase which derived from TRANSFORM-2, while for subsequent time-points i.e. optimization and maintenance were derived from SUSTAIN-1. (10, 11) Furthermore, as shown in Table 23 the average number of sessions per week and devices per session was calculated separately for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The model used the flexible dosing schedule from TRANSFORM-2 and SUSTAIN-1 as it is aligned with the prescribing label. This is in line with submission to other health authorities e.g. for the single technology appraisal of Spravato® at the National Institute for Health and Care Excellence. (25)

Table 26: AIP price of Spravato per unit of 28mg.

Product	Units	Strength	ATC	Price (DKK)	Price per unit (DKK)
Spravato®	1	28 mg	N06AX27	1361,93	1.361,93
Spravato®	2	28 mg	N06AX27	2936,55	1.468,28
Spravato®	3	28 mg	N06AX27	4367,93	1.455,98
Average	-	-	-		1.428,73

5.5.2.2 Drug acquisition SSRI and SNRI

Dosing of the SSRI and SNRI are based on the dosing clinical trials. (10, 11, 13, 14) All patients were initiated, open-label, on one of four OADs from two classes: an SSRI (escitalopram or sertraline), or an SNRI (duloxetine or venlafaxine XR). The maximum daily dosage of oral ADs were used in the model and are in line with the recommended dosages in the Danish treatment recommendation for adult patients with unipolar depression, see table 27. (16) This assumption was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

Treatment with SSRI and SNRI is continuous and patients in long-term treatment with antidepressants (> 2 years) should be considered min. one time during the year with respect to whether treatment indication remains. (16)

Table 27: Dosage of SSRI and SNRI

Oral anti-depressant	Dosage
Duloxetine (SNRI)	120 mg/day
Escitalopram (SNRI)	20 mg/day
Sertraline (SSRI)	200 mg/day
Venlafaxine XR (SSRI)	375 mg/day

The doses described above for SSRI and SNRI constituted the basis for calculating the medicine cost associated with SSRI and SNRI for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The cost of duloxetine, escitalopram, sertraline and venlafaxine was based on the Danish Medicines Agency´s reported AIP prices on medicinpriser.dk. (46) Table 28 shows the price, units, strength and ATC code of the extracted data from medicinpriser.dk.

Table 28: AIP price of the SSRI and SNRI treatments (46)

Product	Units	Strength	ATC	Price (DKK)
Duloxetine, "Accord"	98	60 mg	N06AX21	85,4
Escitalopram, "Teva"	100	20 mg	N06AB10	82,4
Sertraline, Hexal	100	50 mg	N06AB06	38,3
Venlafaxine, "Medical Valley"	100	75 mg	N06AX16	79,4

In the model, the comparator arm is a mix of oral anti-depressants displayed in table 28. An even market share distribution was applied as there is no standard of care (and no treatment specifically approved in this indication) for this population. This assumption only impacts the drug acquisition costs, but as they are similar for all oral ADs the distribution in market share does not have a big impact on the results. Table 29 beneath provides assumptions on the market share as well as the weighted acquisition cost per dosage per 4-week for the SSRI and SNRI. The calculation can be found in the sheet "Drug Cost Oral AD" in the model.

Table 29: Overview of the market share distribution between the OAD, number of doses per week, daily dosage, unit cost per mg and weighted acquisition cost per 4-week.

		Number of doses/week	Daily dosage (mg)	Unit cost	Weighted acquisition cost per 4 week cycle
Drugs	Market share	Acute	Acute	(DKK/mg)	
Duloxetine	25,00%	7	120	0,015	DKK 56,48
Escitalopram	25,00%	7	20	0,041	
Sertraline	25,00%	7	200	0,008	
Venlafaxine	25,00%	7	375	0,008	

5.5.2.3 Administration and monitoring cost Spravato

Spravato® is self-administered but this needs to be performed under the supervision of a healthcare professional. During and after Spravato administration, patients are monitored for sedation and dissociation until the patient is stable based on clinical judgement. Patients will typically need to wait 5 minutes between self-administering each device, and so the typical administration time will be between 5–10 minutes for 56 mg (two devices) and 84 mg (three devices), respectively. Requirements for HCP supervision and post-dose observation is in the SmPC for Spravato® stated to be until the HCP confirms

the patient is clinically stable and is allowed to leave the clinic/facility where Spravato® has been administered. (1) A post hoc analysis of two short-term studies in TRD observed that ≥90% of patients were considered ready for discharge at 90 minutes after administration. (47) Thus, the average observation period after each session was assumed to 90 minutes.
The average administration and monitoring costs for a patient treated with Spravato® nasal spray were estimated to be DKK 537 per session and was applied for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The calculation is available in the sheet "Administration Spravato" in the excel model. This is based on the assumption that three patients can be started-up concurrently within 20-minute intervals (including 5-minute wait in between device administrations) and allowing a total of 90 minutes of monitoring time per patient. This result in the assumption of a 2.5 hour visit where one healthcare professional can observe three patients at the time. There is no need to have fully separate treatment rooms, but it is recommended that the patients are separated by at least a curtain. As stated the total period could be assigned to one HCP e.g. a nurse, however to be conservative the patients self-administration is assumed to be observed by a doctor even though the SmPC only states that the observation could be by a HCP. (1) Thus, with the assumption that three patients can be started-up concurrently a total of 1 hour salary to a doctor and 1.5 hour salary to a nurse responsible for the post-administration observation period where a doctor is not present was used to calculate the cost of 1611 DKK. This was divided by 3 to have the administration and monitoring costs per patient per treatment session of 537 DKK. The hourly salary of a doctor and a nurse was based on Medicine Council´s valuation of unit cost. (44) Table 30 summarizes the administration cost per session applied for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). In addition to the cost outlined in table 30, an extra cost to one additional follow-up visit per 4-week cycle was applied in the base case analysis. The additional cost of the follow-up visit was DKK 390, equal to a half hour consultation with a doctor.

Table 30: Administration and observation resource use and cost applied for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

Resource use	Cost per hour	Total duration required (hours)	Number of patients in cohort	Average cost per session per patient
Doctor "reservelæge"	780	1	3	537 DKK
Nurse	554	1.5		

The assumption regarding three patients being able to get observed at the same time is based on trial investigators' experience with the use of Spravato. Based on trial investigators' experience, the supervision of self-administration of a group of six patients in a clinic could be managed by one or two nurses. As one nurse potentially can manage a group of six patients and on the basis of further dialogue with some of the Swedish investigators who participated in the clinical trial program, it is considered very realistic to be able to treat 3 patients at a time. In addition, as the vast majority of side effects, which the patients are monitored for, are mild and transient, it will be possible to treat several patients sequentially.

Furthermore, administration cost associated with structural changes is not included in the cost analysis as the approval of Spravato for standard treatment of TRD will not require substantial changes to the

current clinical practice and capacity. The requirement of a post-administration observation period after each session and the regular clinical visits with Spravato is not an uncommon practice in Danish psychiatry. In fact, Danish psychiatry have a long standing experience with post-administration observation periods as seen during treatment with the long-acting antipsychotic olanzapine pamoate and electroconvulsive therapy (ECT) (48, 49). Furthermore, regular visits are required, i.e. every second week or monthly, for the maintenance treatment with the licensed long-acting antipsychotic treatments and is a common practice in psychiatry. (50, 51)

In accordance with the summary of product characteristics of Spravato the availability of blood pressure monitoring equipment is generally required in addition to a chair or bed where the patient's head can be rested in a 45° angled position during administration. (1) These elements are readily available in Danish health care facilities and would not be considered as major changes to the infrastructure. Further, there are no specific recruitments to the administration/observation room where Spravato should be self-administered under supervision by a health care professional, but in alignment with the approved risk management plan (RMP) material by DKMA a comfortable and quite room should be considered due to the potential nature of the transient adverse events.(1, 52) Only in patients with clinically significant or unstable cardiovascular or respirator conditions additional precautions are required if this patient group is considered for Spravato treatment. In these patients, Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.

The above-described required practical elements have been confirmed through dialogue with a number of Danish departments. Here it has been reassured that both appropriate rooms, chairs/beds and equipment for blood pressure monitoring equipment is available. Specifically, some departments with access to an ECT unit have considered using these rooms, while others have considered available regular rooms for the treatment. How this should be set up in a large scale should be considered from department to department in accordance with local infrastructure.

5.5.2.4 Administration and monitoring cost SSRI and SNRI

Administration cost associated with SSRI and SNRI is based on the TRIDEN study which reported average healthcare utilization in the first year after TRD, given for patients treated with SSRI or SNRI as first line treatment. As mentioned in section 5.5.1.1, reported outpatient visits and home visits was excluded from the calculation of the MDE health state as it was deemed to be associated with the treatment of SSRI and SNRI. Instead the reported outpatient and home visits will be used to calculate the 4 week administration and monitoring cost associated with SSRI and SNRI. The yearly health care utilization of outpatient visits and home visits within the psychiatric sector which was reported in the TRIDEN study, is available in table 31 and was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The reason for applying the data to the MSM ≥ 9 is that there are no evidence available on the health care utilization of outpatient visits and home visits in a MSM ≥ 9 population or a TRD population consisting only of TRD patients with a severe depressive episode. However, it can reasonably be expected that the MSM ≥ 9 subpopulation would have a higher number of both outpatient visits and home visits. Thus, the assumption is quite conservative.

Table 31: Yearly healthcare utilization of outpatient visits and home visits reported for patients treated with SSRI or SNRI as first line treatment

Type of health care utilization	*SSRI Mean (SD)*	*SNRI Mean (SD)*
Psychiatric contacts		
Outpatient visits	7.0 (13.9)	9.2 (16.1)
Home visits	1.5 (6.0)	1.8 (7.1)

The yearly administration cost resulted in DKK 18.954 assuming even distribution between SSRI and SNRI and using the cost of DKK 1.944, stated in table 17, for an outpatient visit and a home visit. Consequently, this resulted in a cost of DKK 52 per day.

5.5.2.5 Patient and Transportation cost Spravato

Patient cost was for Spravato® calculated on the basis of time used at each treatment session and the average number of treatment sessions per week.
In line with the assumptions for the administration cost it was assumed that a patient would use 20 minutes on the nasal spray administration with a subsequent use of 90 minutes on post-administration observation. Consequently, a patient was assumed to use 110 minutes on each treatment session. (47)
The cost of time used on treatment per 60 minutes was assumed to be 179 DKK, as stated in Medicine Council´s valuation of unit cost. (44) Thus, the average patient cost per treatment session applied in the base case analysis was 328 DKK, see table 32. This assumption was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).
The calculation is available in the sheet "Patient time Spravato" in the model.

Regarding transportation cost, the cost per treatment session was assumed to be 100 DKK, as stated in the Medicine Council´s valuation of unit cost, due to the fact that Spravato® must be administered at the hospital, see table 33. (1, 44) This assumption was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).
The calculation is available in the sheet "Patient time Spravato" in the excel model.

Table 32: Patient cost associated with the treatment of Spravato® in combination with a SSRI or SNRI used in base case for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

	Number of minutes used per session	Cost per hour	Cost per session
Patient time (min)	110	179	328

Table 33: Transportation cost associated with the treatment of Spravato® in combination with a SSRI or SNRI used in base case for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

	Cost per treatment session
Transportation cost	100 DKK

The patient and transportation cost assumptions and approach presented in the tables and paragraphs above was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

5.5.2.6 Patient cost Transportation cost SSRI and SNRI

Patient cost was based on the reported use of healthcare utilization from the RWE study TRIDEN. Further details of the calculation is available under the sheet "Patient time Oral AD" in the model. However, a visit to the hospital was assumed to be the duration of half an hour and the same was assumed for other health care visits, whereas a hospitalization was accounted to be 24 hours. The patient time cost per hour was assumed to be 179 DKK. The yearly and daily calculated cost is available in table 34 and was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The reason for applying the data to the MSM ≥ 9 is that there are no evidence available on the health care utilization in a MSM ≥ 9 TRD population or a TRD population consisting only of TRD patients with a severe depressive episode. However, it can reasonably be expected that the MSM ≥ 9 subpopulation would have a higher patient cost. Thus, the assumption is quite conservative.

Regarding transportation it was also based on the reported use of healthcare utilization from the RWE study TRIDEN. A transportation cost of 100 DKK per healthcare visit was assumed, as stated in the Medicine Council´s valuation of unit cost. Further details of the calculation is available under the sheet "Patient time Oral Ad" in the model. The yearly calculated cost is available in table 35 and was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The reason for applying the data to the MSM ≥ 9 is as stated above.

Table 34: Patient cost associated with the treatment of SSRI and SNRI used in base case for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

	Yearly cost	Daily
Patient time	DKK 40.705	DKK 112

Table 35: Transportation cost associated with the treatment of SSRI and SNRI used in base case for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2)

	Yearly cost	Daily
Transportation cost	DKK 3.015	DKK 8

The patient and transportation cost assumptions and approach presented in the tables and paragraphs above was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

5.5.3 Cost of Adverse Events

The cost of managing the dissociation AE was considered in the base case analysis. The dissociation AE management cost is assumed to be accounting for one doctor follow-up visit, see table 36. Consequently, the cost of DKK 780 was applied which is a conservative assumption based on the AE being transient and occurred at the time of administration. The assumption was applied for the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). The reason for applying the data to the MSM ≥ 9 subpopulation, is that there is no separate safety evidence on the MSM ≥ 9 subpopulation.

Table 36. Cost of Managing dissociation AE for both the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2).

AE	Unit Costs	
	Mean	SE
Dissociation	DKK 780	DKK 195

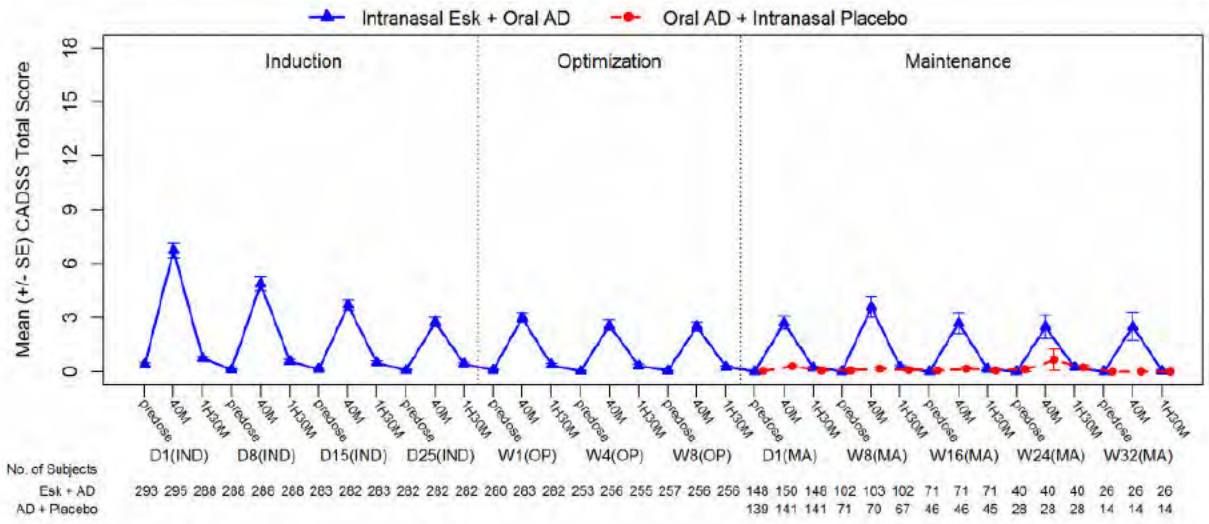
The list of other AEs is available in table 11. However, the cost associated with adverse events are in general found not to be relevant to include and in many cases it is not possible to estimate as for e.g. nasal discomfort, throat irritation, dry mouth and feeling drunk. Furthermore, the requirements for HCP supervision and post-dose observation, until the HCP confirms the patient is clinically stable and is allowed to leave the clinic/facility where SPRAVATO has been administered, is due to the observation of adverse events. Thus, as a cost is assigned to the observation of patients in the model, the cost associated with adverse events is already included. In addition, the adverse events reported are of transient nature which will in many cases resolve within 1.5 hours post-dose and in most cases within the same day. Consequently, we don't find it relevant and reasonable to include cost associated with adverse events. Further detailed description on the nature of observed adverse events is available in the EPAR for Spravato and summarized in the following section.(52) Furthermore, an extensive description of adverse events observed in the clinical trials for Spravato, is available in the clinical part of the submission to the Medicines Council.

The adverse events cost assumptions and approach presented in the tables and paragraphs above was approved by the Medicines Council in the initial evaluation of esketamine for the treatment of TRD, as evident from the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

<u>Dissociation/perceptual changes</u>

Across completed Phase 2 and 3 studies, the most common psychological effects of esketamine have been dissociative/ perceptual changes (including distortion of time and space and illusions), derealization and depersonalization and were measured using CADSS (Clinician Administered Dissociative States Scale). Across the Phase 2 and 3 studies, the following similar pattern of change was observed in the mean CADSS score in esketamine dosing sessions: dissociative/perceptual changes had an onset shortly after the start of dosing, peaked by 40 minutes post-dose, and typically returned to post-dose levels at the 1.5-hour post-dose assessment, see figure 4. Over the course of each Phase 3 study, the peak mean CADSS total score at the 40-minute post-dose time-point in the esketamine + oral AD groups generally decreased with consecutive doses. This attenuation was apparent both in the short-term studies as well as with prolonged exposure in the long-term studies.(52)

Figure 4. Arithmetic Mean (+/- SE) Clinician-administered Dissociative States Scale (CADSS) Total Score Over Time; Induction, Optimization, and Maintenance Phases (SUSTAIN-1)



Psychotic-like symptoms

To capture the extent of treatment-emergent psychotic-like symptoms potentially associated with esketamine administration, the Phase 3 clinical trials included the 4 item Brief Psychiatric Rating Scale (BPRS) + subscale, which assessed suspiciousness, hallucinations, unusual thought content, and conceptual disorganization. Across all studies, a small mean increase in BPRS+ total score from baseline was observed at 40-minute post-dose assessment in esketamine + oral AD treatment groups (mean maximum values of <1 indicating symptoms were `very mild´). After this transient, minimal worsening, mean scores generally returned to pre-dose values at the 1.5-hour post-dose assessment.(52)

Anxiety

TEAE grouped terms related to anxiety (preferred terms of anxiety, anticipatory anxiety, and anxiety disorder) were reported at higher rates in the esketamine + oral AD groups than in the oral AD + intranasal placebo group in the controlled Phase 3 studies/study phases in adults (TRANSFORM-1/TRANSFORM-2: 9.0% vs 5.4%, respectively; DB MA phase of SUSTAIN-1: 7.9% vs 3.4%), but was reported less often in the esketamine + oral AD group for elderly subjects in TRANSFORM-3 (4.2% vs 7.7%). In the Phase 3 studies in TRD, severe anxiety TEAEs were uncommon in the esketamine + oral AD treatment groups (incidence rates of 0.3% to 1.4% across studies/study phases). The TEAE of anxiety only infrequently required rescue treatment (<4% in esketamine + oral AD groups for each study)(52)

Furthermore, the reported frequency of anxiety TEAEs on each dosing day generally decreased after the first week of dosing in the pooled short-term studies TRANSFORM-1/TRANSFORM-1 and the induction phase in SUSTAIN-1.

Transient dizziness or vertigo

Dizziness and vertigo (individual preferred terms) were generally mild or moderate in intensity, non-serious, and not treatment limiting. Across the Phase 3 studies/study phases, both of these individual TEAEs were reported as severe in intensity at incidences of < 3%. No serious individual TEAEs of dizziness or vertigo were reported in esketamine-treated subjects.

Reported TEAEs of dizziness and vertigo following esketamine dosing in the Phase 3 studies were generally transient and self-limiting. Most of these events occurred on the day of dosing, and of those events reported on the day of dosing, almost all (>95%) resolved spontaneously the same day. Decreases in the reporting frequencies of dizziness and vertigo were observed early in treatment (i.e., on Days 1 through 8) compared with subsequent nasal spray dosing sessions in the short-term studies TRANSFORM-1/TRANSFORM-2 and the long-term studies SUSTAIN-1 and SUSTAIN-2.(52)

Sedation/Somnolence

Across all Phase 2 and 3 studies, sedation was one of the most common effects associated with esketamine treatment. Sedation was measured using the MOAA/S (Modified Observer's Assessment of Alertness/Sedation) scale. Based on the MOAA/S, sedative effects were generally mild, had an onset shortly after the start of the dose and typically resolved by 1 to 1.5 hours post-dose. TEAEs of somnolence (12.1-21.1%) and sedation (4.2-10.1%) were primarily mild or moderate in severity, occurred on the day of intranasal dosing and resolved spontaneously the same day, with the median duration under 2 hours across dosing sessions. These TEAEs led to treatment discontinuation in isolated cases and reported as a SAE in only 1 subject across all Phase 2 and 3 studies. Rates of TEAEs of somnolence were relatively stable over time during longer-term treatment.(52)

Post-dose Gastrointestinal Symptoms of Nausea and Vomiting

Across the Phase 2 and 3 studies in TRD, nausea and vomiting were the most frequent gastrointestinal TEAEs in esketamine-treated subjects In the controlled Phase 3 studies, nausea and vomiting were reported at higher rates for the esketamine + oral AD groups than for the oral AD + intranasal placebo group. However, in the pooled TRANSFORM-1/TRANSFORM-2 studies, ~85% of TEAEs of nausea and vomiting were reported on the day of dosing for esketamine treated subjects, with 81% of reports of nausea and 98% of reports of vomiting resolving the same day. The same pattern was seen in elderly subjects and for each phase of the relapse prevention study SUSTAIN-1. TEAEs of nausea and vomiting were primarily mild or moderate in severity, transient, and self limited with the median duration not exceeding 1 hour in most subjects across dosing sessions. Furthermore, rates of reported nausea and vomiting decreased over time.(52)

Nasal Tolerability and Sense of Smell

Across Phase 2 and 3 studies there were no nasal exam findings or Nasal Symptom Questionnaire evidence to support an impact on nasal anatomy or function including the sense of smell assessed by the UPSIT (University of Pennsylvania Smell Identification Test) and the Smell Threshold Test scores. Most esketamine-treated subjects had no findings upon nasal examination, detected abnormalities were mostly of mild severity (consisting mainly of nasal erythema, nasal discharge, nasal crust), with the exception of a few moderate findings and no findings that were severe. The frequency of these symptoms

did not increase with continued administration. Nasal tolerability of esketamine nasal spray was good, also after long term treatment.(52)

Cardiovascular safety

Heart rate, blood pressure and ECG

Transient, primarily asymptomatic, increases in systolic and diastolic BP were observed following esketamine administration in all Phase 2 and 3 studies in TRD, with maximum mean changes typically observed within 40 minutes of dosing and mean BP values subsequently returning to, or close to, pre-dose values within the 1.5-hour post-dose time-point. Between 90% and 100% of the reported TEAE preferred term of increased BP occurred on the day of dosing in the Phase 3 studies/study phases and of these, >93% resolved spontaneously the same day.(52)

Observed mean increases in pulse rate following esketamine administration were not clinically meaningful in any of the Phase 3 studies. Esketamine administration did not produce any meaningful changes in ECG parameters and had no effect on cardiac repolarization.(52)

Overall, due to the transient and self-limiting nature of the cardiovascular effects observed in clinical trials, the overall impact on the risk-benefit balance of the product is considered low. The SmPC and PL, as well as the Healthcare Professional Guide and Patient Guide, provide information to the prescriber and the patient on how to manage the risk. A checklist for readiness to leave will be provided to aid HCP in determining when a patient is deemed stable and should safely be allowed to return home following esketamine nasal spray administration.(52)

5.6 CUA Results for the full TRD population (clinical question 1)

5.6.1 Base Case results

The base case clinical and economic outcomes for the full TRD population (clinical question 1) are presented in Table 37 and Table 38. Over a five-year time horizon, esketamine nasal spray plus oral AD was associated with additional 0.344 QALYs compared with oral AD. The incremental cost for esketamine nasal spray plus oral AD in the base case with restricted societal perspective was DKK 45.680 for the full TRD population (clinical question 1). However, over the five-year time horizon, esketamine nasal spray plus oral AD was estimated to have lower disease management costs, in particular saving DKK 32.784 compared with oral AD and also lower administration cost, saving DKK 3.971. When including productivity loss the incremental cost for esketamine nasal spray plus oral AD was DKK -96.395 and when looking separately at the Indirect costs for esketamine nasal spray plus oral AD, it was DKK 142.075 lower compared with oral AD.

Table 37. Effectiveness Outcomes (Discounted) for the full TRD population (clinical question 1)

Health State	ESK + Oral AD	Oral AD	Difference
Total life years	**4,522**	**4,513**	**0,009**
MDE	2,967	3,581	-0,615
Response	0,245	0,296	-0,051

Health State	ESK + Oral AD	Oral AD	Difference
Remission	0,538	0,394	0,144
Recovery	0,772	0,242	0,530
Total QALYs	**2,543**	**2,198**	**0,344**
MDE	1,133	1,368	-0,235
Response	0,202	0,244	-0,042
Remission	0,496	0,363	0,133
Recovery	0,711	0,223	0,488
AE	0,000	0,000	0,000

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode

Table 38. Cost Outcomes (Discounted) for the full TRD population (clinical question 1)

Cost Outcomes	ESK + Oral AD	Oral AD	Difference
BASE CASE RESULTS			
Total costs	**DKK 561.386**	**DKK 515.706**	**DKK 45.680**
Treatment Acquisition	DKK 85.720	DKK 3.325	DKK 82.394
Treatment Administration and Monitoring	DKK 278.886	DKK 282.857	-DKK 3.971
Disease Management	DKK 196.733	DKK 229.517	-DKK 32.784
AE Management	DKK 47	DKK 7	DKK 40
INDIRECT COST RESULTS			
Productivity Loss	DKK 1.103.539	DKK 1.245.614	-DKK 142.075

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; RW = real-world

Furthermore, esketamine nasal spray plus oral AD yielded greater clinical benefits, which translated into higher QALYs and savings, in disease management costs compared with oral AD. Table 39 shows the incremental cost-effectiveness outcomes. Esketamine nasal spray plus oral AD resulted in cost savings and higher QALYs compared with oral AD from the societal perspective (esketamine nasal spray plus oral AD was dominant).

Table 39. Incremental Cost Effectiveness Outcomes for the full TRD population (clinical question 1)

Outcomes	ESK + Oral AD vs. Oral AD
BASE CASE RESULTS	
Incremental QALYs	0,344
Incremental costs, restricted societal perspective	**DKK 45.680**
ICER—cost per QALY gained, restricted societal perspective	DKK 132.691
INDIRECT COST RESULTS	
Incremental costs, societal perspective	-DKK 96.395
ICER—cost per QALY gained, societal perspective	-DKK 280.011

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RW = real-world

Figure 5 shows the flow of patients through the years for the full TRD population (clinical question 1) treated with esketamine + oral AD, whereas figure 6 shows the flow of patients through the years for the full TRD population (clinical question 1) treated with Oral AD. Comparing the two figures it is evident that more patients are in the recovery, remission and response health states when treated esketamine + oral AD. Furthermore, a graph reporting the share of patients that are in subsequent treatment as time in the model progresses was explicitly requested by the Medicines Council and Expert Committee. These graph are available in the health economic model under the sheet "Results".

Figure 5. Markov Trace for the full TRD population (clinical question 1) treated with esketamine + oral AD

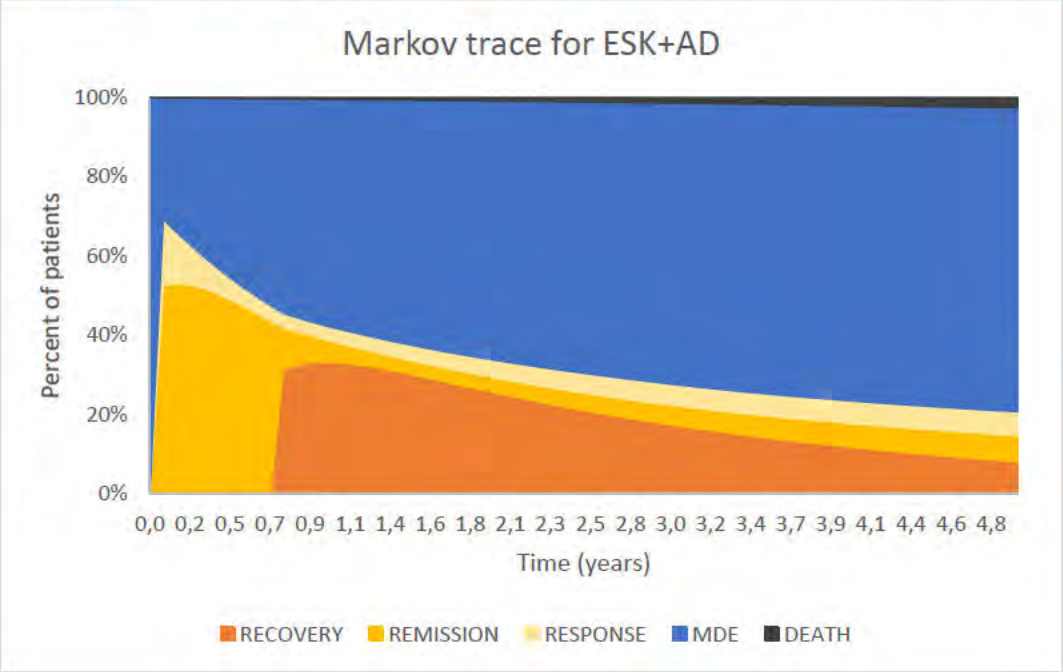
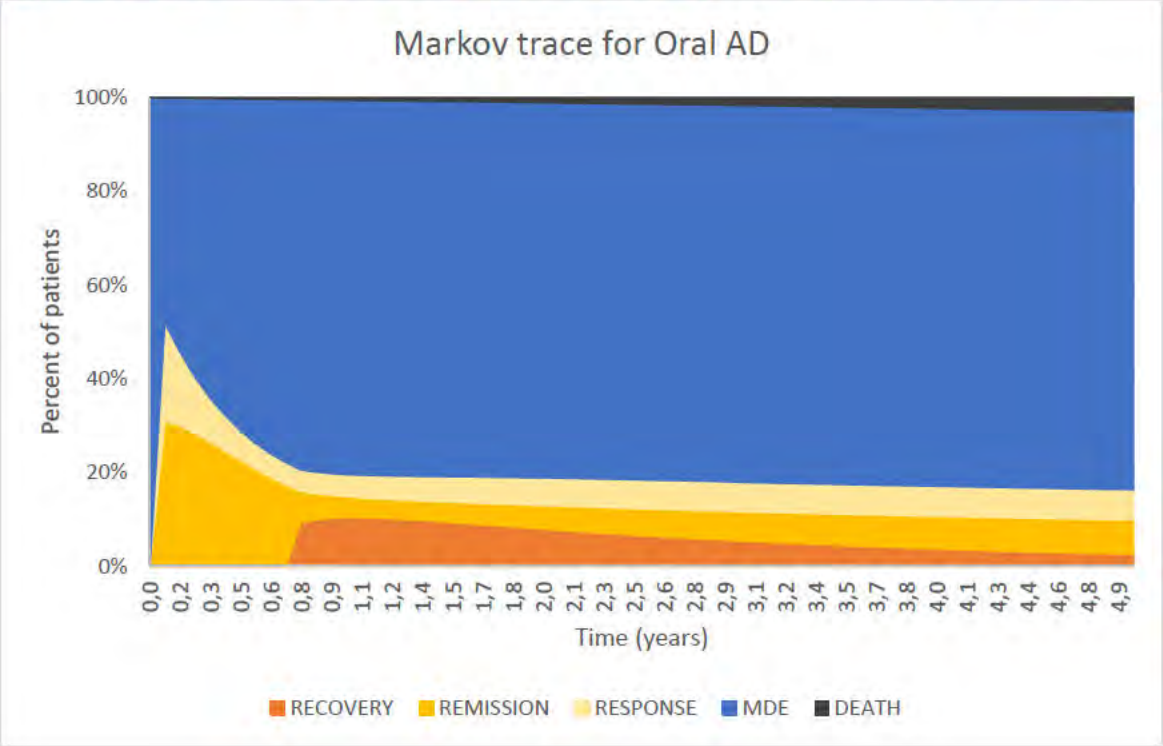


Figure 6. Markov Trace for the full TRD population (clinical question 1) treated with Oral AD



5.6.2 Deterministic Sensitivity Analysis

For the full TRD population (clinical question 1), a deterministic sensitivity analysis (DSA) was conducted by varying parameters from their base-case value, one parameter at a time, see table 40. The analysis evaluated lower and upper bounds for each model parameter considered. The bounds were derived from descriptive statistics when available (e.g., 95% confidence intervals [CI]), or assumed ±10% from the parameter's mean value.

Table 40. Deterministic Sensitivity Analyses Assumptions for the full TRD population (clinical question 1)

Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Settings						
Time Horizon	5 years	3 years	7 years	Assumption	DKK 51.289	DKK 43.723
Discount Rate for Cost	3.50%	0.00%	5.00%	Assumption	DKK 44.578	DKK 46.094
Discount Rate for Health	3.50%	0.00%	5.00%	Assumption	DKK 45.680	DKK 45.680
Age of Patients at Start of Analysis	45.7	22.4	69.0	95% CI(53)	DKK 45.680	DKK 45.680
% Female	61.90%	55.71%	68.09%	+/- 10% of base case	DKK 45.633	DKK 46.235
Clinical Inputs						
Remission Probability, ESK + Oral AD	0.525	0.427	0.622	95% CI(53)	DKK 46.797	DKK 44.562

Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Remission Probability, Oral AD	0.310	0.219	0.401	95% CI(37)	DKK 41.521	DKK 49.838
Response to Remission Probabilities, ESK + Oral AD	0.199	0.111	0.288	Assumption	DKK 48.146	DKK 44.402
Response to Remission Probabilities, Oral AD	0.124	0.063	0.185	Assumption	DKK 44.504	DKK 46.436
Response Probability, ESK + Oral AD	0.168	0.095	0.241	95% CI(53)	DKK 44.364	DKK 46.995
Response Probability, Oral AD	0.210	0.130	0.290	95% CI(37)	DKK 43.628	DKK 47.731
Relapse Probability, ESK + Oral AD	0.056	0.008	0.103	95% CI(53)	DKK 33.173	DKK 53.464
Relapse Probability, Oral AD	0.123	0.054	0.193	95% CI(54)	DKK 58.708	DKK 38.332
Loss of Response Probability, ESK + Oral AD	0.042	0.000	0.092	95% CI(53)	DKK 46.221	DKK 45.210
Loss of Response Probability, Oral AD	0.149	0.058	0.239	95% CI(54)	DKK 48.290	DKK 44.351
Recurrence Probability, ESK + Oral AD and Oral AD	0.029	0.000	0.066	95% CI(53)	DKK 22.825	DKK 56.291
Remission Probability, Subsequent Treatment Mix	0.004	0.002	0.006	95% CI(39)	DKK 44.629	DKK 46.674
Response Probability, Subsequent Treatment Mix	0.008	0.004	0.012	95% CI(39)	DKK 45.215	DKK 46.116
Relapse Probability, Subsequent Treatment Mix	0.042	0.021	0.063	95% CI(39)	DKK 46.547	DKK 45.158
Loss of Response Probability, Subsequent Treatment Mix	0.104	0.053	0.155	95% CI(39)	DKK 46.344	DKK 45.390
Treatment Discontinuation Probability, ESK + Oral AD	Table 10	Lower 95% CI	Upper 95% CI	95% CI(55)	DKK 53.744	DKK 41.344
AE Probability during the Acute Treatment Phase, ESK + Oral AD	Table 11	-10%	10%	Assumption	DKK 45.675	DKK 45.684
AE Probability during the Acute Treatment Phase, Oral AD	Table 11	-10%	10%	Assumption	DKK 45.680	DKK 45.679
Costs Inputs						
AE Management Costs	Table 36	-10%	10%	Assumption	DKK 45.676	DKK 45.684
Direct Medical Costs in MDE Health State	DKK 4.582	DKK 2.337	DKK 6.828	95% CI; Assumption	DKK 63.681	DKK 27.678
Direct Medical Costs in Response Health State	DKK 2.614	DKK 1.333	DKK 3.895	95% CI; Assumption	DKK 46.528	DKK 44.831
Direct Medical Costs in Remission Health State	DKK 646	DKK 330	DKK 963	95% CI; Assumption	DKK 44.488	DKK 46.275
Direct Medical Costs in Recovery Health State	DKK 646	DKK 330	DKK 963	95% CI; Assumption	DKK 43.490	DKK 47.869
Unit cost of device, Esketamine, ESK + Oral AD	DKK 1.428,73	DKK 1.285,86	DKK 1.571,60	+/- 10% of base case	DKK 37.440	DKK 53.919
Monitoring costs, Esketamine, ESK + Oral AD	DKK 965,17	DKK 868,65	DKK 1.061,68	95% CI; Assumption	DKK 43.522	DKK 47.837

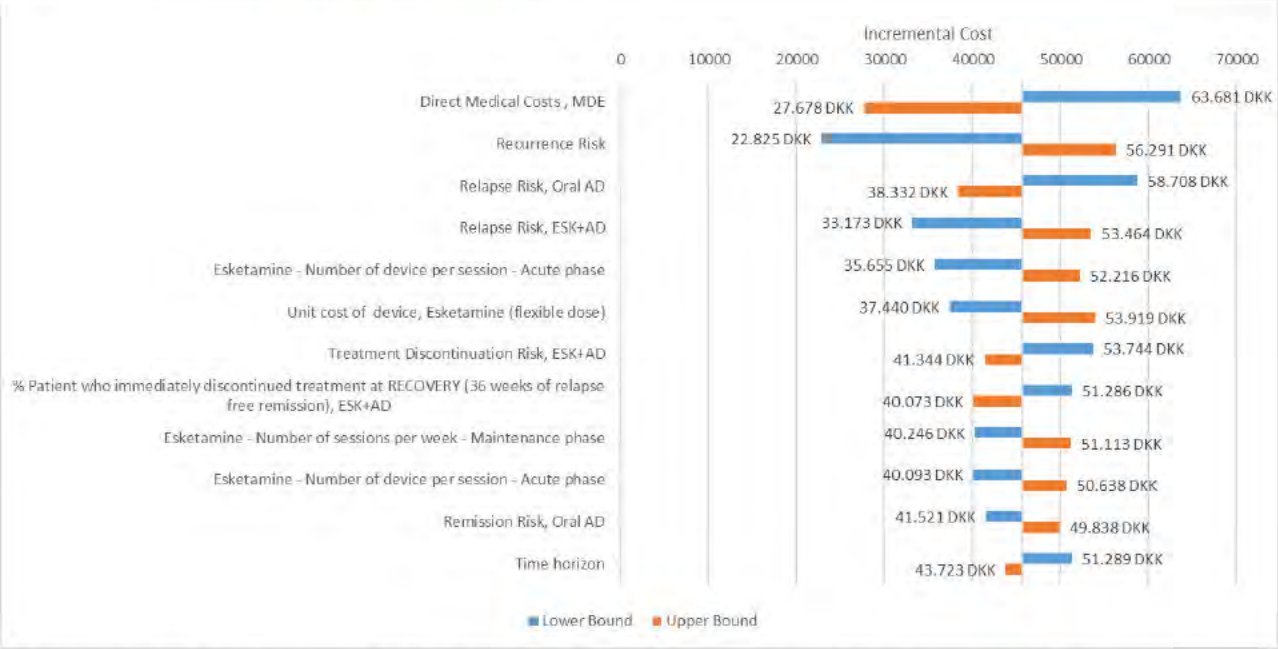
Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Esketamine—Number of sessions per week—Acute Phase, ESK + Oral AD	1.85	1.67	2.04	Assumption	DKK 42.299	DKK 49.060
Esketamine—Number of sessions per week—Week 5-8, ESK + Oral AD	0.99	0.89	1.09	Assumption	DKK 44.441	DKK 46.918
Esketamine—Number of sessions per week—While in Remission, ESK + Oral AD	0.71	0.64	0.78	Assumption	DKK 40.246	DKK 51.113
Esketamine—Number of sessions per week—While in Recovery, ESK + Oral AD	0.67	0.61	0.74	Assumption	DKK 45.334	DKK 46.025
Esketamine—Number of devices per session—Acute Phase, ESK + Oral AD	2.53	2.00	3.00	Assumption	DKK 40.093	DKK 50.638
Esketamine—Number of devices per session—Week 5-8, ESK + Oral AD	2.61	2.00	3.00	Assumption	DKK 43.395	DKK 47.169
Esketamine—Number of devices per session—While in Remission, ESK + Oral AD	2.61	2.00	3.00	Assumption	DKK 35.655	DKK 52.216
Esketamine—Number of devices per session—While in Recovery, ESK + Oral AD	2.57	2.00	3.00	Assumption	DKK 45.072	DKK 46.136
Unit Cost, Oral AD	Table 28	-10%	10%	Assumption	DKK 45.679	DKK 45.680
Excess mortality for TRD patients, MDE	0.0047	0.002	0.007	Assumption	DKK 45.171	DKK 46.186
Excess mortality for TRD patients, Response	0.0024	0.001	0.004	Assumption	DKK 45.664	DKK 45.695

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode; RW=real-world; CI = confidence intervals

*Only relevant with societal perspective

Some of the deterministic sensitivity results are displayed in the tornado diagram in Figure 7, which visually demonstrate that the results are quite robust.

Figure 7. Tornado Diagram—ESK + Oral AD vs. Oral AD (Restricted Societal Perspective) for the full TRD population (clinical question 1)



Abbreviation: AD = antidepressant; ESK = esketamine; ICER = incremental cost-effectiveness ratio; MDE = major depressive episode

5.6.3 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was also conducted for the full TRD population (clinical question 1) to account for multivariate stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probability distributions. Table 41 shows the details of standard errors (SE) and distributions used for the PSA. One thousand replications were used, each one of which sampled individual parameter values from the assigned probability distribution.

Table 41. PSA Parameters for the full TRD population (clinical question 1)

Parameters	Mean	SE	Distribution
Baseline Characteristics			
Age of Patients at Start of Analysis	45.7	11.89	Normal
Clinical Inputs			
Remission Probability, ESK + Oral AD	0.525	0.050	Beta
Remission Probability, Oral AD	0.310	0.046	Beta
Response to Remission Probabilities, ESK + Oral AD	0.199	0.045	Beta
Response to Remission Probabilities, Oral AD	0.124	0.031	Beta
Response Probability, ESK + Oral AD	0.168	0.037	Beta
Response Probability, Oral AD	0.210	0.041	Beta
Relapse Probability, ESK + Oral AD	0.056	0.024	Beta
Relapse Probability, Oral AD	0.123	0.035	Beta

Parameters	Mean	SE	Distribution
Loss of Response Probability, ESK + Oral AD	0.042	0.025	Beta
Loss of Response Probability, Oral AD	0.149	0.046	Beta
Recurrence Probability, ESK + Oral AD and Oral AD	0.029	0.018	Beta
Remission Probability, Subsequent Treatment Mix	0.004	0.001*	Beta
Response Probability, Subsequent Treatment Mix	0.008	0.002*	Beta
Relapse Probability, Subsequent Treatment Mix	0.042	0.010*	Beta
Loss of Response Probability, Subsequent Treatment Mix	0.104	0.026*	Beta
Treatment Discontinuation Probability, ESK + Oral AD	0.70	0.175	Beta
Utility Inputs			
Utilities	Table 13	Table 13	Beta
Disutilities of AE	Table 12	Table 12	Normal
Costs Inputs			
AE Management Costs	Table 36	Table 36*	Gamma
Direct Medical Costs in MDE Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Response Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Remission Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Recovery Health State	Table 15	Table 15*	Gamma
Monitoring costs, Esketamine, ESK + Oral AD	Table 25	Table 25	Gamma

*Assumed 25% of mean

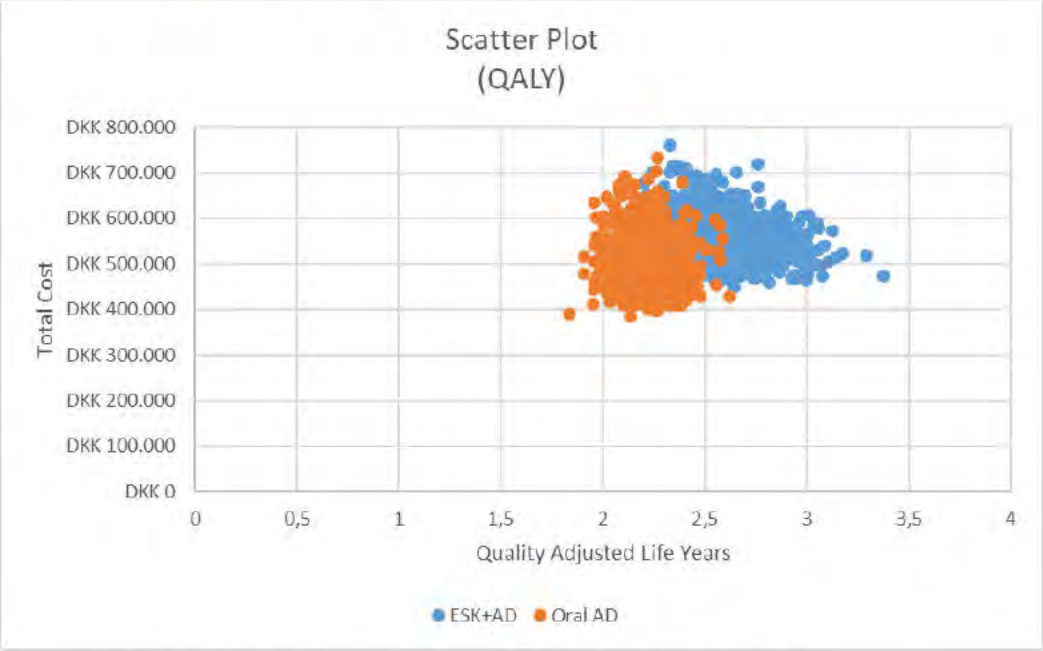
Results of the PSA for the model are displayed in Table 42 and in the cost-effectiveness scatterplots for 1,000 iterations of the PSA (Figure 8).

Table 42. Average outcomes from the simulations for the full TRD population (clinical question 1)

Outcomes	ESK + Oral AD	Oral AD
Life years (LYs)	4,503	4,494
QALYs	2,568	2,214
Costs	DKK 558.019	DKK 513.120
Incremental outcomes: ESK+AD vs. comparators		
LY	0,009	
QALY	0,354	
Cost	DKK 44.898	
ICER		
DKK/LY	DKK 5.024.765	
DKK/QALY	DKK 126.922	

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year

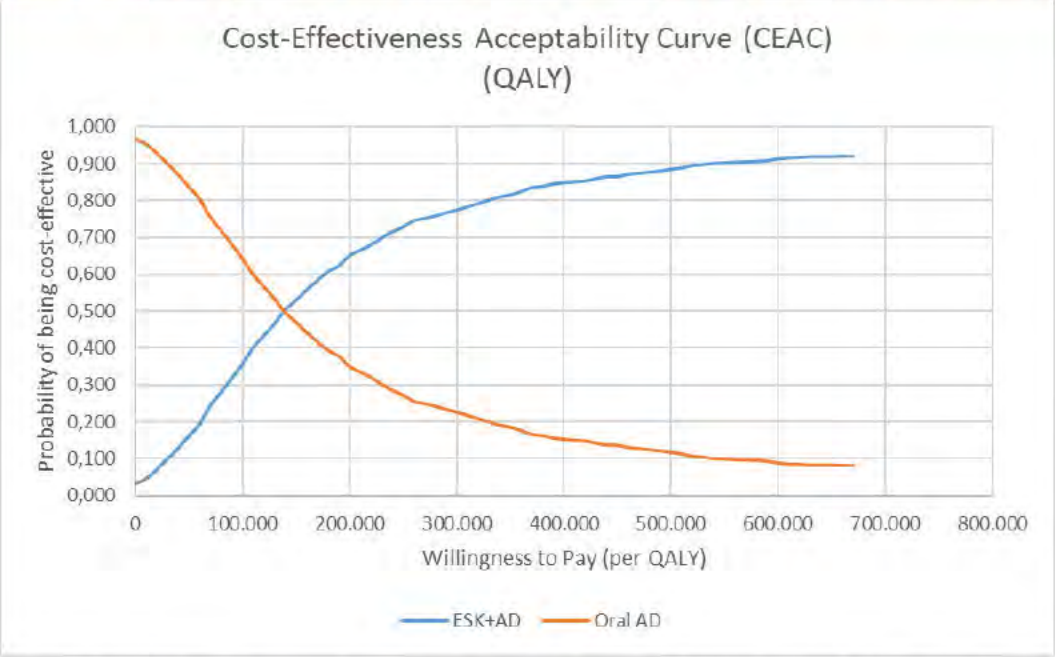
Figure 8. Cost-effectiveness Scatterplot—ESK + Oral AD vs. Oral AD (Societal Perspective) for the full TRD population (clinical question 1)



Abbreviation: AD = antidepressant; ESK = esketamine; QALY = quality-adjusted life year

Figure 9 presents the cost-effectiveness acceptability curve for the full TRD population.

Figure 9. Cost-effectiveness Acceptability Curve for the full TRD population (clinical question 1)



Abbreviation: AD = antidepressant; ESK = esketamine; QALY = quality-adjusted life year; RW = real-world

5.7 CUA Results for the MSM ≥ 9 subpopulation (clinical question 2)

5.7.1 Base Case results

The base case clinical and economic outcomes for the MSM ≥ 9 subpopulation (clinical question 2) are presented in Table 43 and Table 44. Over a five-year time horizon, esketamine nasal spray plus oral AD was associated with additional 0.514 QALYs compared with oral AD. The incremental cost for esketamine nasal spray plus oral AD in the base case with restricted societal perspective was DKK 24.015 for the MSM ≥ 9 subpopulation (clinical question 2). However, over the five-year time horizon, esketamine nasal spray plus oral AD was estimated to have lower disease management costs, in particular saving DKK 59.311 compared with oral AD and also lower administration cost saving DKK 3.107.

When including productivity loss the incremental cost for esketamine nasal spray plus oral AD was DKK -183.758 and when looking separately at the indirect costs for esketamine nasal spray plus oral AD it was DKK 207.774 lower compared with oral AD.

Table 43. Effectiveness Outcomes (Discounted) for the MSM ≥ 9 subpopulation (clinical question 2)

Health State	ESK + Oral AD	Oral AD	Difference
Total life years	**4,522**	**4,508**	**0,014**
MDE	2,994	3,911	-0,917
Response	0,254	0,296	-0,043
Remission	0,526	0,288	0,238
Recovery	0,748	0,012	0,735
Total QALYs	**2,547**	**2,033**	**0,514**
MDE	1,147	1,498	-0,351
Response	0,220	0,257	-0,037
Remission	0,488	0,267	0,221
Recovery	0,693	0,011	0,682
AE	0,000	0,000	0,000

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode

Table 44. Cost Outcomes (Discounted) for the MSM ≥ 9 subpopulation (clinical question 2)

Cost Outcomes	ESK + Oral AD	Oral AD	Difference
BASE CASE RESULTS			
Total costs	**DKK 613.978**	**DKK 589.962**	**DKK 24.015**
Treatment Acquisition	DKK 89.715	DKK 3.322	DKK 86.393
Treatment Administration and Monitoring	DKK 279.433	DKK 282.541	-DKK 3.107
Disease Management	DKK 244.782	DKK 304.093	-DKK 59.311
AE Management	DKK 47	DKK 7	DKK 40
INDIRECT COST RESULTS			
Productivity Loss	DKK 1.110.790	DKK 1.318.564	-DKK 207.774

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; RW = real-world

Furthermore, esketamine nasal spray plus oral AD yielded greater clinical benefits, which translated into higher QALYs and savings, in disease management costs compared with oral AD. Table 45 shows the incremental cost-effectiveness outcomes. Esketamine nasal spray plus oral AD resulted in cost savings and higher QALYs compared with oral AD from the societal perspective (esketamine nasal spray plus oral AD was dominant).

Table 45. Incremental Cost Effectiveness Outcomes for the MSM ≥ 9 subpopulation (clinical question 2)

Outcomes	ESK + Oral AD vs. Oral AD
BASE CASE RESULTS	
Incremental QALYs	0,514
Incremental costs, restricted societal perspective	**DKK 24.015**
ICER—cost per QALY gained, restricted societal perspective	DKK 46.739
INDIRECT COST RESULTS	
Incremental costs, societal perspective	-DKK 183.758
ICER—cost per QALY gained, societal perspective	-DKK 357.632

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RW = real-world

Figure 10 shows the flow of patients through the years for the the MSM ≥ 9 subpopulation (clinical question 2) treated with esketamine + oral AD, whereas figure 11 shows the flow of patients through the years for the MSM ≥ 9 subpopulation (clinical question 2) treated with Oral AD. Comparing the two figures it is evident that more patients are in the recovery, remission and response health states when treated esketamine + oral AD.

Figure 10. Markov Trace for the MSM ≥ 9 subpopulation (clinical question 2) treated with esketamine + oral AD

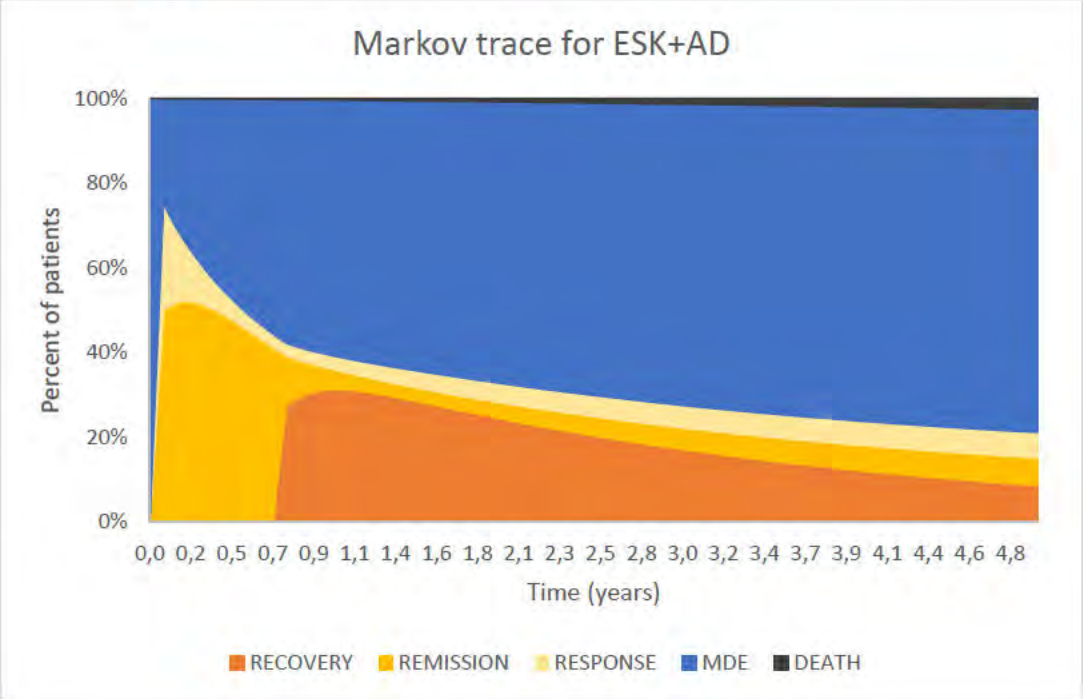
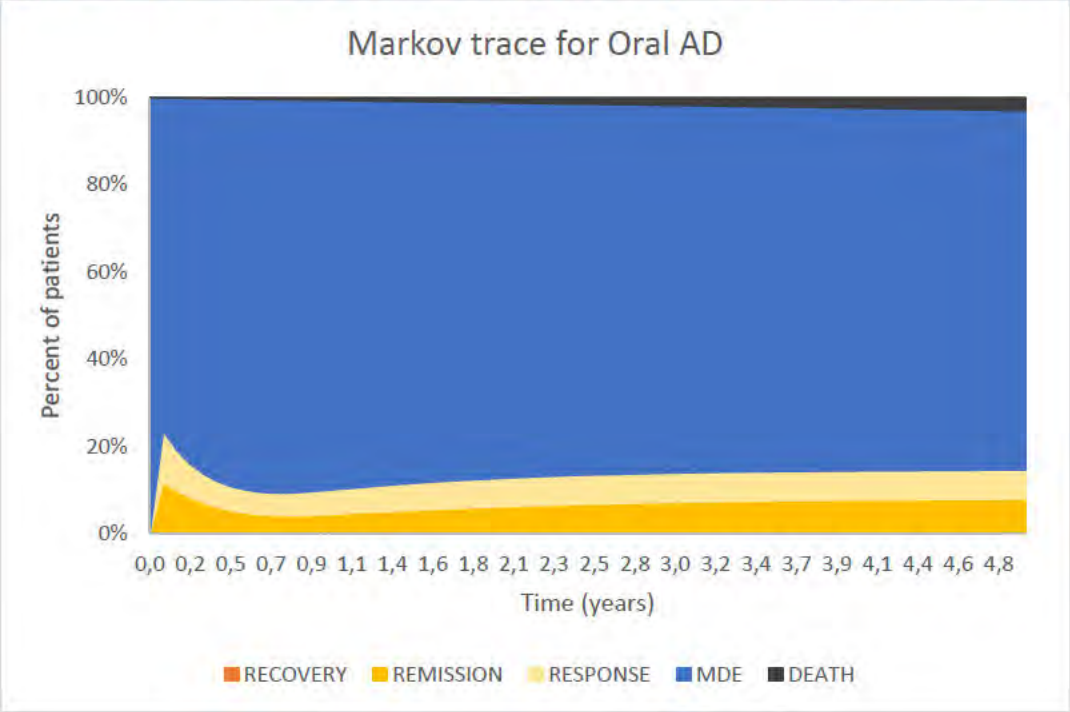


Figure 11. Markov Trace for the MSM ≥ 9 subpopulation (clinical question 2) treated with Oral AD



5.7.2 Deterministic Sensitivity Analysis

A deterministic sensitivity analysis (DSA) was conducted for the MSM ≥ 9 subpopulation (clinical question 1) by varying parameters from their base-case value, one parameter at a time, see table 46. The analysis evaluated lower and upper bounds for each model parameter considered. The bounds were derived from descriptive statistics when available (e.g., 95% confidence intervals [CI]), or assumed ±10% from the parameter's mean value.

Table 46. Deterministic Sensitivity Analyses Assumptions for the MSM ≥ 9 subpopulation (clinical question 2)

Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Settings						
Time Horizon	5 years	3 years	7 years	Assumption	DKK 34.249	DKK 19.974
Discount Rate for Cost	3.50%	0.00%	5.00%	Assumption	DKK 21.381	DKK 25.029
Discount Rate for Health	3.50%	0.00%	5.00%	Assumption	DKK 24.015	DKK 24.015
Age of Patients at Start of Analysis	45.7	22.4	69.0	95% CI(53)	DKK 24.015	DKK 24.015
% Female	61.90%	55.71%	68.09%	+/- 10% of base case	DKK 23.915	DKK 25.246
Clinical Inputs						
Remission Probability, ESK + Oral AD	[redacted]	[redacted]	[redacted]	95% CI(53)	DKK 26.513	DKK 21.518

Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Remission Probability, Oral AD	[redacted]	[redacted]	[redacted]	95% CI(37)	DKK 22.962	DKK 25.069
Response to Remission Probabilities, ESK + Oral AD	[redacted]	[redacted]	[redacted]	Assumption	DKK 26.895	DKK 22.297
Response to Remission Probabilities, Oral AD	[redacted]	[redacted]	[redacted]	Assumption	DKK 23.956	DKK 24.053
Response Probability, ESK + Oral AD	[redacted]	[redacted]	[redacted]	95% CI(53)	DKK 23.473	DKK 24.558
Response Probability, Oral AD	[redacted]	[redacted]	[redacted]	95% CI(37)	DKK 23.071	DKK 24.960
Relapse Probability, ESK + Oral AD	[redacted]	[redacted]	[redacted]	95% CI(53)	DKK 5.391	DKK 35.499
Relapse Probability, Oral AD	[redacted]	[redacted]	[redacted]	95% CI(54)	DKK 26.355	DKK 23.017
Loss of Response Probability, ESK + Oral AD	[redacted]	[redacted]	[redacted]	95% CI(53)	DKK 24.476	DKK 23.690
Loss of Response Probability, Oral AD	[redacted]	[redacted]	[redacted]	95% CI(54)	DKK 24.896	DKK 23.575
Recurrence Probability, ESK + Oral AD and Oral AD	[redacted]	[redacted]	[redacted]	95% CI(53)	-DKK 11.236	DKK 43.033
Remission Probability, Subsequent Treatment Mix	0.004	0.002	0.006	95% CI(39)	DKK 22.065	DKK 25.859
Response Probability, Subsequent Treatment Mix	0.008	0.004	0.012	95% CI(39)	DKK 23.160	DKK 24.819
Relapse Probability, Subsequent Treatment Mix	0.042	0.021	0.063	95% CI(39)	DKK 25.660	DKK 23.037
Loss of Response Probability, Subsequent Treatment Mix	0.104	0.053	0.155	95% CI(39)	DKK 25.249	DKK 23.481
Treatment Discontinuation Probability, ESK + Oral AD	Table 10	Lower 95% CI	Upper 95% CI	95% CI(55)	DKK 31.453	DKK 19.957
AE Probability during the Acute Treatment Phase, ESK + Oral AD	Table 11	-10%	10%	Assumption	DKK 24.011	DKK 24.020
AE Probability during the Acute Treatment Phase, Oral AD	Table 11	-10%	10%	Assumption	DKK 24.016	DKK 24.015
Costs Inputs						
AE Management Costs	Table 36	-10%	10%	Assumption	DKK 24.011	DKK 24.019
Direct Medical Costs in MDE Health State	DKK 5.654	DKK 2.884	DKK 8.425	95% CI; Assumption	DKK 57.155	-DKK 9.125
Direct Medical Costs in Response Health State	DKK 3.226	DKK 1.645	DKK 4.806	95% CI; Assumption	DKK 24.898	DKK 23.133
Direct Medical Costs in Remission Health State	DKK 797	DKK 407	DKK 1.188	95% CI; Assumption	DKK 21.697	DKK 25.228
Direct Medical Costs in Recovery Health State	DKK 797	DKK 407	DKK 1.188	95% CI; Assumption	DKK 20.268	DKK 27.763
Unit cost of device, Esketamine, ESK + Oral AD	DKK 1.428,73	DKK 1.285,86	DKK 1.571,60	+/- 10% of base case	DKK 15.377	DKK 32.654
Monitoring costs, Esketamine, ESK + Oral AD	DKK 965,17	DKK 868,65	DKK 1.061,68	95% CI; Assumption	DKK 21.848	DKK 26.183

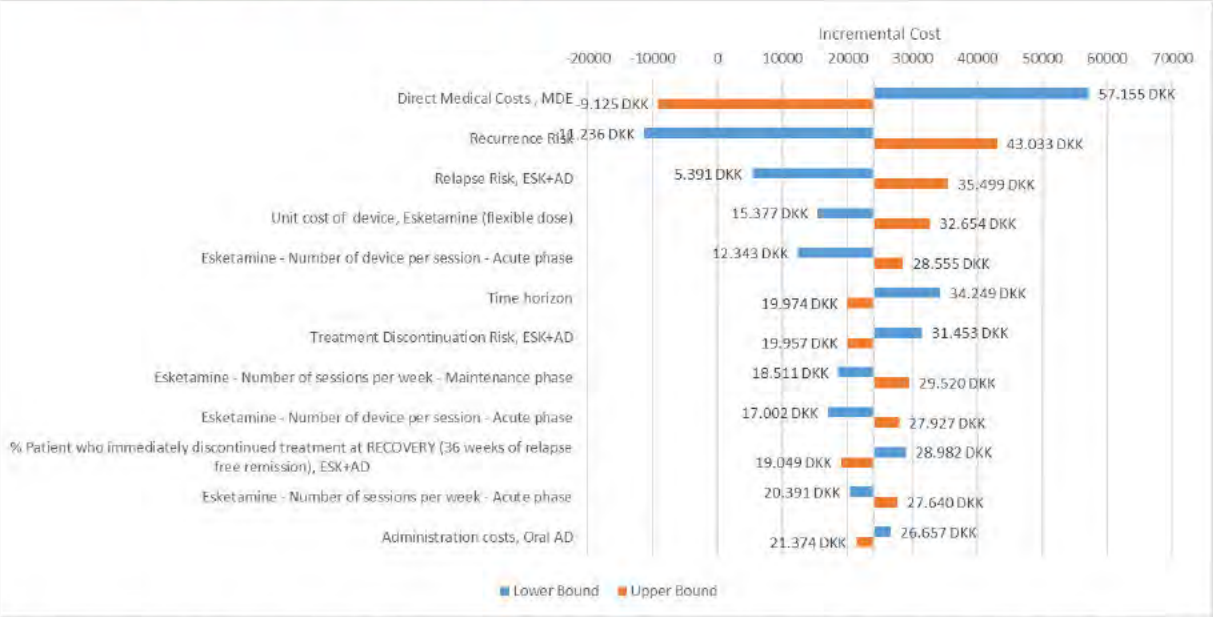
Parameters	Base Case	Lower Bound	Upper Bound	Source	Lower (Incremental cost)	Upper (Incremental cost)
Esketamine—Number of sessions per week—Acute Phase, ESK + Oral AD	1,92	1,73	2,11	Assumption	DKK 20.391	DKK 27.640
Esketamine—Number of sessions per week—Week 5-8, ESK + Oral AD	1,00	0,90	1,10	Assumption	DKK 22.639	DKK 25.392
Esketamine—Number of sessions per week—While in Remission, ESK + Oral AD	0,72	0,65	0,80	Assumption	DKK 18.511	DKK 29.520
Esketamine—Number of sessions per week—While in Recovery, ESK + Oral AD	0,62	0,56	0,68	Assumption	DKK 23.715	DKK 24.316
Esketamine—Number of devices per session—Acute Phase, ESK + Oral AD	2,64	2,00	3,00	Assumption	DKK 17.002	DKK 27.927
Esketamine—Number of devices per session—Week 5-8, ESK + Oral AD	2,72	2,00	3,00	Assumption	DKK 21.096	DKK 25.151
Esketamine—Number of devices per session—While in Remission, ESK + Oral AD	2,72	2,00	3,00	Assumption	DKK 12.343	DKK 28.555
Esketamine—Number of devices per session—While in Recovery, ESK + Oral AD	2,67	2,00	3,00	Assumption	DKK 23.415	DKK 24.315
Unit Cost, Oral AD	Table 28	-10%	10%	Assumption	DKK 26.657	DKK 21.374
Excess mortality for TRD patients, MDE	0.0047	0.002	0.007	Assumption	DKK 23.151	DKK 24.875
Excess mortality for TRD patients, Response	0.0024	0.001	0.004	Assumption	DKK 24.007	DKK 24.024

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode; RW=real-world; CI = confidence intervals

*Only relevant with societal perspective

Some of the deterministic sensitivity results are displayed in the tornado diagram in Figure 12, which visually demonstrate that the results are quite robust for the MSM ≥ 9 subpopulation.

Figure 12. Tornado Diagram—ESK + Oral AD vs. Oral AD (Restricted Societal Perspective) for the MSM ≥ 9 subpopulation (clinical question 2)



Abbreviation: AD = antidepressant; ESK = esketamine; ICER = incremental cost-effectiveness ratio; MDE = major depressive episode

5.7.3 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was also conducted for the MSM ≥ 9 subpopulation (clinical question 2), to account for multivariate stochastic uncertainty in the model. The uncertainty in the individual parameters was characterized using probability distributions. Table 47 shows the details of standard errors (SE) and distributions used for the PSA. One thousand replications were used, each one of which sampled individual parameter values from the assigned probability distribution.

Table 47. PSA Parameters for the MSM ≥ 9 subpopulation (clinical question 2)

Parameters	Mean	SE	Distribution
Baseline Characteristics			
Age of Patients at Start of Analysis	45.7	11.89	Normal
Clinical Inputs			
Remission Probability, ESK + Oral AD	[redacted]	[redacted]	Beta
Remission Probability, Oral AD	[redacted]	[redacted]	Beta
Response to Remission Probabilities, ESK + Oral AD	[redacted]	[redacted]	Beta
Response to Remission Probabilities, Oral AD	[redacted]	[redacted]	Beta
Response Probability, ESK + Oral AD	[redacted]	[redacted]	Beta
Response Probability, Oral AD	[redacted]	[redacted]	Beta
Relapse Probability, ESK + Oral AD	[redacted]	[redacted]	Beta
Relapse Probability, Oral AD	[redacted]	[redacted]	Beta
Loss of Response Probability, ESK + Oral AD	[redacted]	[redacted]	Beta
Loss of Response Probability, Oral AD	[redacted]	[redacted]	Beta

Parameters	Mean	SE	Distribution
Recurrence Probability, ESK + Oral AD and Oral AD	[redacted]	[redacted]	Beta
Remission Probability, Subsequent Treatment Mix	0.004	0.001*	Beta
Response Probability, Subsequent Treatment Mix	0.008	0.002*	Beta
Relapse Probability, Subsequent Treatment Mix	0.042	0.010*	Beta
Loss of Response Probability, Subsequent Treatment Mix	0.104	0.026*	Beta
Treatment Discontinuation Probability, ESK + Oral AD	0,70	0,175	Beta
Utility Inputs			
Utilities	Table 13	Table 13	Beta
Disutilities of AE	Table 12	Table 12	Normal
Costs Inputs			
AE Management Costs	Table 36	Table 36*	Gamma
Direct Medical Costs in MDE Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Response Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Remission Health State	Table 15	Table 15*	Gamma
Direct Medical Costs in Recovery Health State	Table 15	Table 15*	Gamma
Monitoring costs, Esketamine, ESK + Oral AD	Table 25	Table 25	Gamma

*Assumed 25% of mean

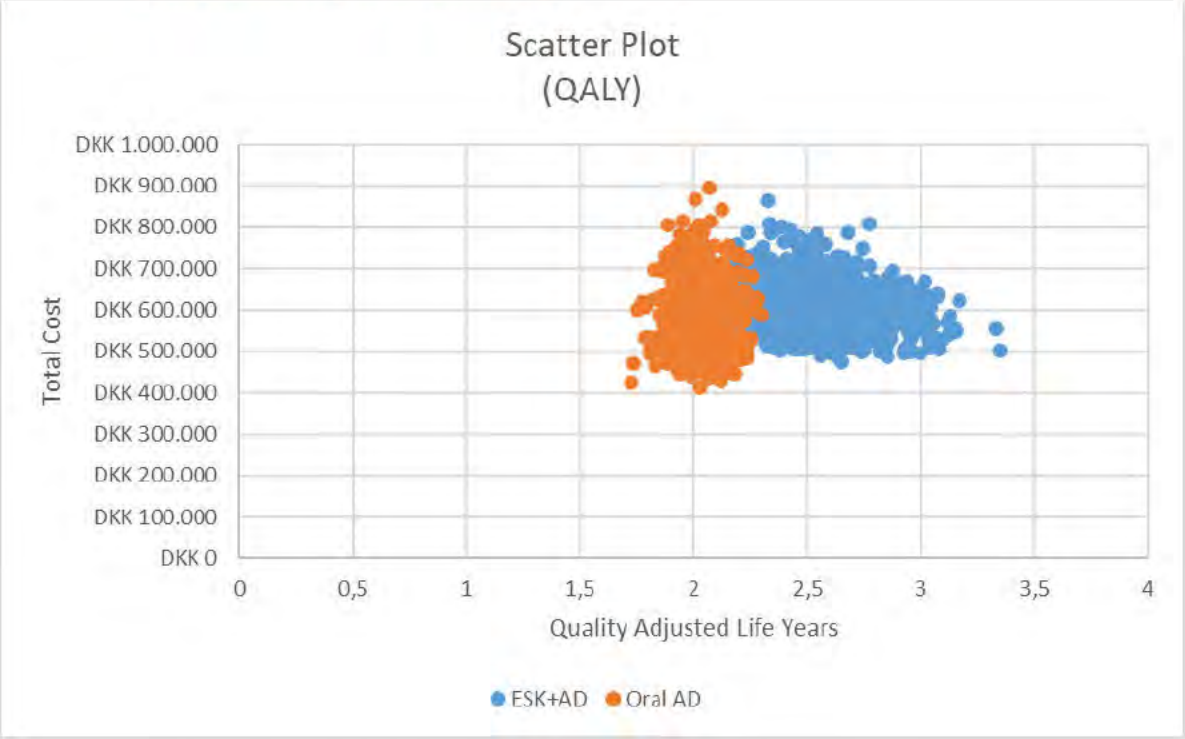
Results of the PSA for the model are displayed in Table 48 and in the cost-effectiveness scatterplots for 1,000 iterations of the PSA (Figure 13).

Table 48. Average outcomes from the simulations for the MSM ≥ 9 subpopulation (clinical question 2)

Outcomes	ESK + Oral AD	Oral AD
Life years (LYs)	4,502	4,489
QALYs	2,574	2,031
Costs	DKK 609.907	DKK 589.437
Incremental outcomes: ESK+AD vs. comparators		
LY	0,014	
QALY	0,543	
Cost	DKK 20.470	
ICER		
DKK/LY	DKK 1.496.628	
DKK/QALY	DKK 37.704	

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year

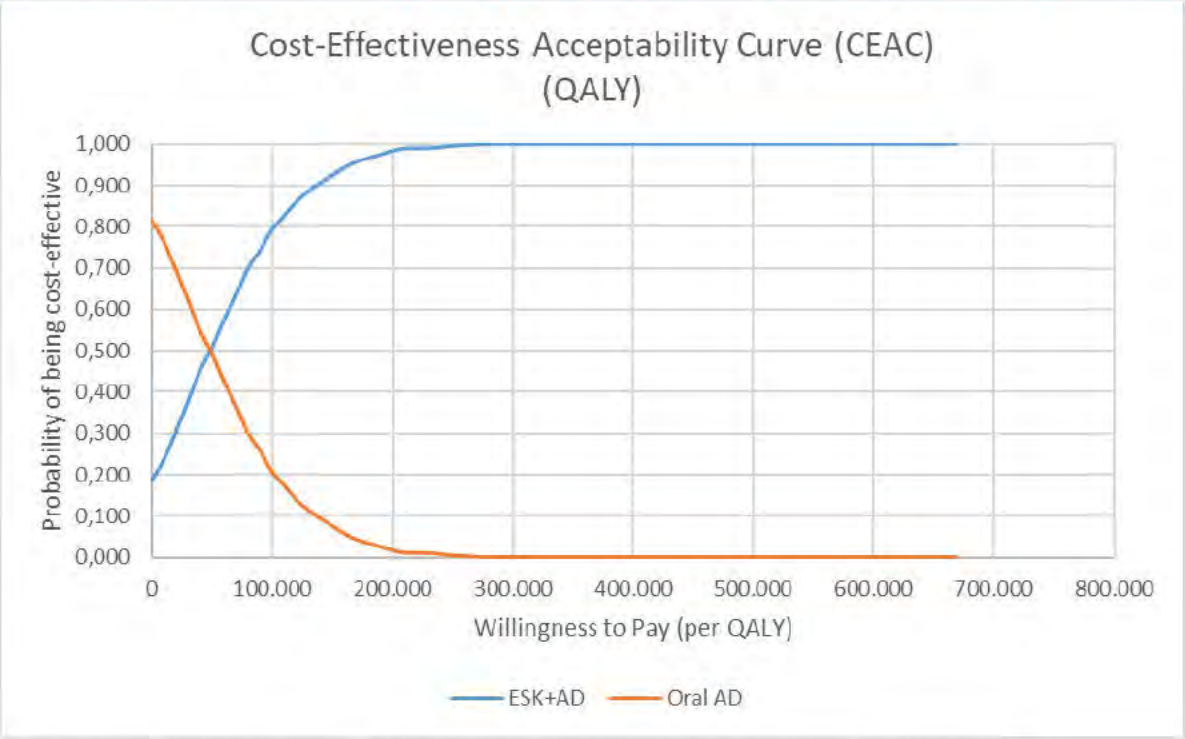
Figure 13. Cost-effectiveness Scatterplot—ESK + Oral AD vs. Oral AD (Societal Perspective) for the MSM ≥ 9 subpopulation (clinical question 2)



Abbreviation: AD = antidepressant; ESK = esketamine; QALY = quality-adjusted life year

Figure 14 presents the cost-effectiveness acceptability curve, for the MSM ≥ 9 subpopulation.

Figure 14. Cost-effectiveness Acceptability Curve for the MSM ≥ 9 subpopulation (clinical question 2)



Abbreviation: AD = antidepressant; ESK = esketamine; QALY = quality-adjusted life year; RW = real-world

6 Budget impact

6.1 Budget impact perspective

The budget impact analysis was conducted for a period of 5 years and based on the base case results of the cost-analysis and estimated number of patients treated with Spravato in the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2). However, the budget impact analyses excluded patient costs as well as the costs are not discounted as advised by Medicine Council.

6.2 Population

The eligible adults with in the full TRD population (clinical question 1) in a population of 4.687.000 equivalent to the Danish adult population in DK in 2021 is estimated to be 6.170, see Figure 15. This is calculated by multiplying the prevalence of MDD (3%) with the amount of adults in the Danish population. (8, 56-59). Adults who have MDD are thus estimated to be 140.610, of which the frequency of adults diagnosed with MDD or treated for MDD (65.3%) is used to estimate that 91.818 adults in Denmark can be diagnosed with MDD or is being treated for MDD.(60) The prevalence of MDD patients who have failed / had no response to 2 or more ADs corresponding to the TRD definition is reported by Gronemann et al. 2018 as 14%. (4) This results in 12.855 adults estimated to have TRD. Results from Danish RWE evidence study conducted by Janssen was used to determine the percentage of TRD population with the severity of moderate and severe MDD, which is 60%. This is in line with a study by Ellervik et al. 2014 which estimated a percentage of 54% and Gronemann et al. 2018 which report 57.7% in DK. (4, 59) Applying the severity percentage of 60% to the 12.855 patients with TRD resulted in a prevalence of adults with moderate to severe TRD in the Danish population of 7.713. Furthermore, as the indication approved by EMA is Spravato® in combination with a SSRI or SNRI, the proportion of TRD patients is needed to determine patients eligible for treatment with Spravato®. Results from a Danish RWE evidence study called TRIDEN conducted by an external expert group and sponsored by Janssen was used to determine the percentage of moderate to severe TRD population receiving an SSRI or SNRI as first line treatment which was estimated to 80%, see Appendix C.

Conclusively, there are 6.170 patients with moderate to severe TRD and receiving a SSRI or SNRI which are eligible for treatment with Spravato® in the full TRD population (clinical question 1) in 2021. The amount of patients eligible for Spravato® in the following years are available in table 49 and calculated using the population project in Denmark as reported by Statistics Denmark. (56) Further details on the calculation is available in Appendix C.

However, for the full MSM ≥ 9 subpopulation (clinical question 2) it is assumed that there are 1.000 patients which are eligible for treatment with Spravato each year, see table 49. This assumption is based on the Scientific Committee, in the initial evaluation of Spravato, stating: "a small proportion of patients who have tried several treatment alternatives without success can try treatment with esketamine. This estimate is approx. 1000 patients." This statement is available at page 34 in the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1.(61)

Figure 15. Estimated number of moderate to severe TRD patients in the full TRD population (clinical question 1) eligible for treatment with Spravato® in 2021.

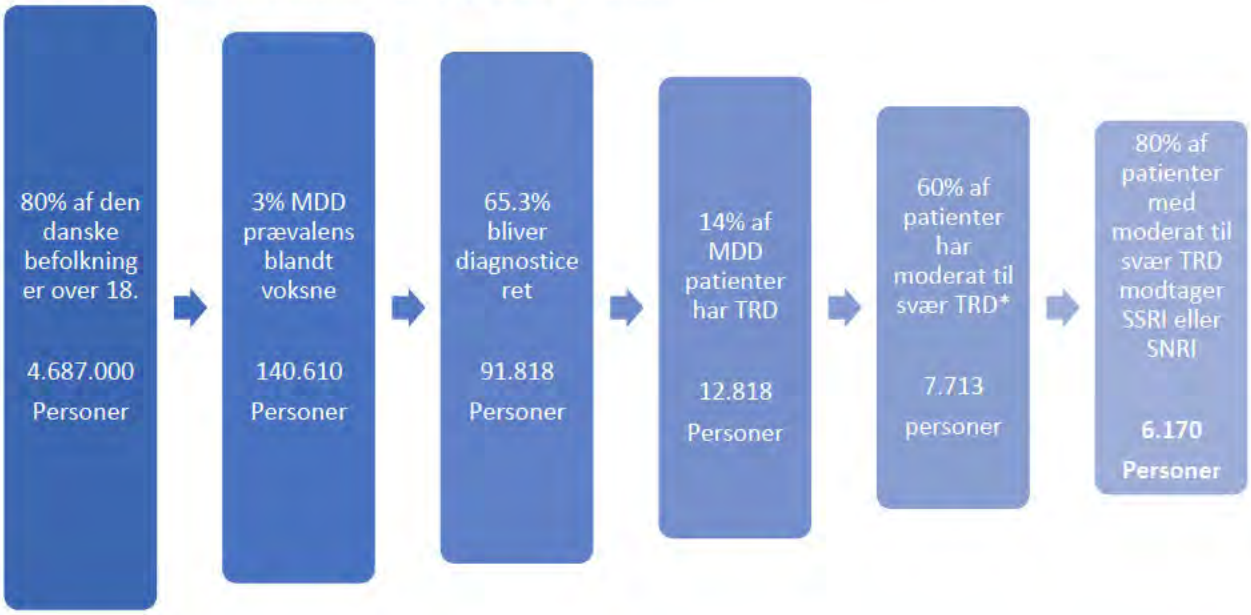


Table 49. Estimated number of TRD patients in the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation (clinical question 2) eligible for treatment with Spravato® in 2021-2025

Year	2021	2022	2023	2024	2025
Number of patients – Full TRD population (clinical question 1)	6152	6185	6218	6250	6281
Number of patients – MSM ≥ 9 subpopulation (clinical question 2)	1000	1000	1000	1000	1000

6.3 Assumption on market share

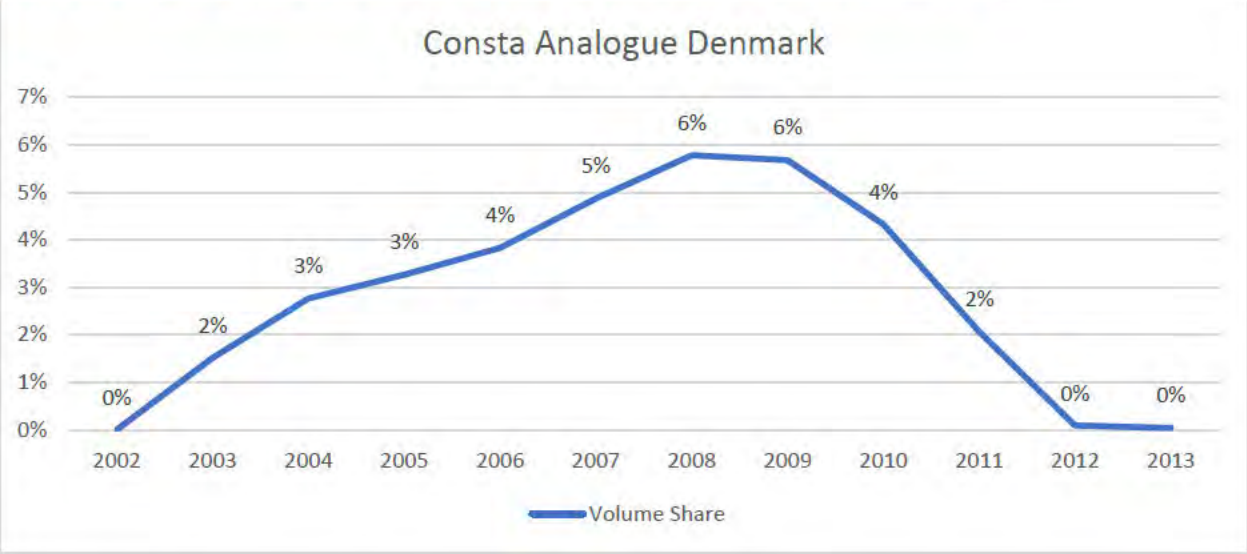
The assumption on market share is first and foremost based on the estimated number of TRD patients in the full TRD population (clinical question 1) and the MSM ≥ 9 subpopulation that are eligible for Spravato® treatment in the period 2021-2025 as described in the section above and Table 49.

6.3.1 Full TRD population (clinical question 1) market share

To estimate the proportion of TRD patients who will receive Spravato® treatment in the full TRD population (clinical question 1) at each year, a benchmark on the market uptake of Risperdal Consta® in Denmark was used. The source of the market uptake was obtained from in market sales.
Risperdal Consta® is an antipsychotic treatment which is administered by deep intramuscular (IM) deltoid or gluteal injection and was introduced to a market where standard treatment was oral administered antipsychotics.(62) Consequently, it resembles the market conditions which Spravato® is introduced to in

the therapeutic area of treatment resistant depression. The market uptake of Risperdal Consta® is illustrated in Figure 16.

Figure 16. Risperdal Consta® market share in antipsychotic market after introduction



In addition to the Risperdal Consta® market share uptake, the proportion of moderate to severe TRD patients which is treated with a SSRI or SNRI and receive concomitant treatment with anti-psychotics is used to estimate the expected market share of Spravato® for the full TRD population (clinical question 1). Results from the TRIDEN study shows that 10.5% of the TRD patients, which received two different treatments after TRD diagnosis, receives concomitant anti-psychotic treatment, see Appendix C.

However, patients who received one treatment after TRD diagnosis (in line with the indication that Spravato® will be used for in the full TRD population "clinical question 1" i.e. as first treatment after TRD diagnosis) less than 1% is receiving concomitant anti-psychotic treatment, see Appendix C.
Based on the descriptions above, the market share for the full TRD population (clinical question 1) was estimated to be placed between the market share uptake of Risperdal Consta® and the 10.5% concomitant treatment use reported by TRIDEN for the first three years.

As Spravato® provides significant clinically improvement compared to the use of SSRI and SNRI as well as being a new innovative treatment to the Danish market, which currently does not have an approved standard treatment for TRD, a forecast is conducted with a market share increase from 4% in 2021 to 16% in 2025 for the full TRD population (clinical question 1). Thus, the uptake is quite aggressive as less than 1% currently is receiving concomitant treatment, and Spravato® will be used as concomitant treatment. The tables 50 and 51 illustrates the current market in the full TRD population (clinical question 1) without Spravato® approved as standards treatment whereas Table 52 and 53 shows the full TRD population (clinical question 1) market with Spravato® approved as standards treatment.

More specifically, 4% in 2021 is assumed based on the expectation that few regional clinics 5-10 will initiate start up with Spravato®. The market share increases to 8% the following year as we expect the experience the first year will positively result in a higher usage in 2022 as well as Spravato® being

available for the full year of 2022. The market share will then increase with 3% from 2022 to 2023 and 2023 to 2024 due to the assumption that satellite clinics to the regional clinics will be set-up and ready to use Spravato® treatment with the supporting experience from the region clinics. Lastly, we expect the market share in the full TRD population (clinical question 1) to flattening out from 2024 and onwards which is the reason that a 2% increase is expected from 2024 to 2025.

Table 50: Market share (%) in current market of the full TRD population (clinical question 1) without Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	0,0%	0,0%	0,0%	0,0%	0,0%
SSRI or SNRI	100,0%	100,0%	100,0%	100,0%	100,0%
Total	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**

Table 51: Number of TRD patient in current market of the full TRD population (clinical question 1) without Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	0	0	0	0	0
SSRI or SNRI	6.152	6.185	6.218	6.250	6.281
Total	6.152	6.185	6.218	6.250	6.281

Table 52: Market share (%) in current market of the full TRD population (clinical question 1) with Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	4,0%	8,0%	11,0%	14,0%	16,0%
SSRI or SNRI	96,0%	92,0%	89,0%	86,0%	84,0%
Total	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**

Table 53: Number of TRD patient in current market of the full TRD population (clinical question 1) with Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	246	495	684	875	1.005
SSRI or SNRI	5.906	5.690	5.534	5.375	5.276
Total	6.152	6.185	6.218	6.250	6.281

6.3.2 MSM ≥ 9 subpopulation (clinical question 2) market share

The number of TRD patients who will receive Spravato® treatment in the MSM ≥ 9 population (clinical question 2) at each year is assumed to be equal to the uptake in the full TRD population (clinical question 1). This is based on the assumption that the capacity of the initial few regional clinics (5-10), which will initiate start up with Spravato®, will remain the same regardless of the whether the patient come from the full TRD population (clinical question 1) or the MSM ≥ 9 subpopulation (clinical question 2). Likewise, the increased number of patients, who will receive Spravato® treatment in the MSM ≥ 9 population, in the subsequent years are based on the assumption that satellite clinics to the regional clinics will be set-up and begin treatment.

However, as it is assumed that there are 1.000 patients which are eligible for treatment with Spravato each year in the MSM ≥ 9 subpopulation (clinical question 2), the market share percentage is higher than in the full TRD population (clinical question 1). In addition, there is a cap on the number of TRD patients with a MSM ≥ 9 score, which can receive Spravato each year i.e. 1.000.

The tables 54 and 55 illustrates the current market in the MSM ≥ 9 subpopulation (clinical question 2) without Spravato® approved as standards treatment whereas Table 56 and 57 shows MSM ≥ 9 subpopulation (clinical question 2) market with Spravato® approved as standards treatment.

Table 54: Market share (%) in current market of the MSM ≥ 9 subpopulation (clinical question 2) without Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	0,0%	0,0%	0,0%	0,0%	0,0%
SSRI or SNRI	100,0%	100,0%	100,0%	100,0%	100,0%
Total	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**

Table 55: Number of TRD patient in current market of the MSM ≥ 9 subpopulation (clinical question 2) without Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	0	0	0	0	0
SSRI or SNRI	1.000	1.000	1.000	1.000	1.000
Total	1.000	1.000	1.000	1.000	1.000

Table 56: Market share (%) in current market of the MSM ≥ 9 subpopulation (clinical question 2) with Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	24,7%	49,6%	68,6%	87,7%	100,0%
SSRI or SNRI	75,3%	50,4%	31,4%	12,3%	0,0%
Total	**100,0%**	**100,0%**	**100,0%**	**100,0%**	**100,0%**

Table 57: Number of TRD patient in current market of the MSM ≥ 9 subpopulation (clinical question 2) with Spravato® recommended as standard treatment

Regimen	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Spravato® + SSRI or SNRI	247	496	686	877	1.000
SSRI or SNRI	753	504	314	123	0
Total	1.000	1.000	1.000	1.000	1.000

7 Budget impact results

7.1 Budget impact results for the full TRD population (clinical question 1)

The results of the base case budget impact analysis for the full TRD population (clinical question 1) with the introduction of Spravato® in combination with a SSRI or SNRI is shown in Table 58 and the budget impact including indirect cost is shown in table 59.

The adoption of Spravato®, in combination with a SSRI or SNRI, as standard treatment to the market is associated with a slight increase in resource use for the treatment of TRD patients who currently do not have an effective and approved standard treatment. In 2021 the budget impact was DKK 13.352.354 which increased to DKK 54.526.079 in 2025 due to the increase in patients treated.

- The result can be found in the sheet "Budget impact – base case" in the excel model. It is worth noting that the inclusion of patients needs to be set at 0% in the "Settings" sheet and then the model should be run.

Table 58: Base case results for the budget impact analysis for the full TRD population (clinical question 1)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	DKK 13.352.354	DKK 26.825.896	DKK 37.099.850	DKK 47.467.942	DKK 54.526.079
Drug	DKK 20.579.215	DKK 41.345.210	DKK 57.179.865	DKK 73.159.608	DKK 84.037.907
Administration	DKK 1.369.484	DKK 2.751.398	DKK 3.805.146	DKK 4.868.549	DKK 5.592.467
Medical costs	-DKK 8.606.296	-DKK 17.290.705	-DKK 23.912.811	-DKK 30.595.593	-DKK 35.144.934
AEs	DKK 9.952	DKK 19.993	DKK 27.651	DKK 35.378	DKK 40.638
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

Thus, the recommendation of Spravato® in combination with a SSRI or SNRI as standard treatment for the full TRD population (clinical question 1), consisting of adults with moderate to severe TRD who have failed on at least two antidepressants, will give patients the possibility to get a new innovative treatment which provides fast and increased response, remission and improved quality of life which will translate into improvement in patient social and occupational functioning. Furthermore, this will have a positive impact on not only the patients themselves, but also their family, friends, and carers. In addition, the budgetary expenses in the regions related to hospitalization will decrease.

Furthermore, the introduction of Spravato will lower the societal financial expenditure associated with treatment of TRD patient in full TRD population, if indirect cost are taking into consideration, as shown in table 59.

Table 59: Results for the budget impact analysis including indirect costs for treatment of the full TRD population (clinical question 1)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-DKK 23.940.244	-DKK 48.097.773	-DKK 66.518.568	-DKK 85.108.148	-DKK 97.763.108
Drug	DKK 20.579.215	DKK 41.345.210	DKK 57.179.865	DKK 73.159.608	DKK 84.037.907
Administration	DKK 1.369.484	DKK 2.751.398	DKK 3.805.146	DKK 4.868.549	DKK 5.592.467
Medical costs	-DKK 8.606.296	-DKK 17.290.705	-DKK 23.912.811	-DKK 30.595.593	-DKK 35.144.934
AEs	DKK 9.952	DKK 19.993	DKK 27.651	DKK 35.378	DKK 40.638
Indirect costs to patients	-DKK 37.292.597	-DKK 74.923.669	-DKK 103.618.419	-DKK 132.576.090	-DKK 152.289.187
Indirect costs to caregivers	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

7.2 Budget impact results for the MSM ≥ 9 subpopulation (clinical question 2)

The results of the base case budget impact analysis for the MSM ≥ 9 subpopulation (clinical question 2) with the introduction of Spravato® in combination with a SSRI or SNRI, is shown in Table 60 and the budget impact including indirect cost is shown in table 61.

The adoption of Spravato®, in combination with a SSRI or SNRI, as standard treatment to the market is associated with a slight increase in resource use for the treatment of TRD patients with a MSM ≥ 9 score who currently do not have an effective and approved standard treatment. In 2021 the budget impact was DKK 7.470.663 which increased to DKK 30.245.598 in 2025 due to the increase in patients treated.

- The result can be found in the sheet "Budget impact – base case" in the excel model. It is worth noting that the inclusion of patients needs to be set at 0% in the "Settings" sheet and then the model should be run.

Table 60: Base case results for the budget impact analysis for the MSM ≥ 9 subpopulation (clinical question 2)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	DKK 7.470.663	DKK 15.001.816	DKK 20.748.480	DKK 26.525.389	DKK 30.245.598
Drug	DKK 21.579.320	DKK 43.333.372	DKK 59.932.849	DKK 76.619.692	DKK 87.365.669
Administration	DKK 1.430.767	DKK 2.873.119	DKK 3.973.709	DKK 5.080.091	DKK 5.792.578
Medical costs	-DKK 15.549.384	-DKK 31.224.674	-DKK 43.185.739	-DKK 55.209.756	-DKK 62.952.972
AEs	DKK 9.960	DKK 20.000	DKK 27.661	DKK 35.363	DKK 40.322
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

Thus, the recommendation of Spravato® in combination with a SSRI or SNRI as standard treatment for the MSM ≥ 9 subpopulation (clinical question 2), will give patients the possibility to get a new innovative treatment which provides fast and increased response, remission and improved quality of life which will translate into improvement in patient social and occupational functioning. Furthermore, this will have a positive impact on not only the patients themselves, but also their family, friends, and carers. In addition, the budgetary expenses in the regions related to hospitalization will decrease.

In addition, the introduction of Spravato will lower the societal financial expenditure associated with treatment of TRD patient in MSM ≥ 9 subpopulation, if indirect costs are taking into consideration, as shown in table 61.

Table 61: Results for the budget impact analysis including indirect costs for treatment of the MSM ≥ 9 subpopulation (clinical question 2)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-DKK 47.001.657	-DKK 94.383.893	-DKK 130.539.014	-DKK 166.884.425	-DKK 190.290.108
Drug	DKK 21.579.320	DKK 43.333.372	DKK 59.932.849	DKK 76.619.692	DKK 87.365.669
Administration	DKK 1.430.767	DKK 2.873.119	DKK 3.973.709	DKK 5.080.091	DKK 5.792.578
Medical costs	-DKK 15.549.384	-DKK 31.224.674	-DKK 43.185.739	-DKK 55.209.756	-DKK 62.952.972
AEs	DKK 9.960	DKK 20.000	DKK 27.661	DKK 35.363	DKK 40.322
Indirect costs to patients	-DKK 54.472.319	-DKK 109.385.710	-DKK 151.287.494	-DKK 193.409.814	-DKK 220.535.705
Indirect costs to caregivers	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

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9 Appendix A

Discontinuation calculations

The number of patients who discontinue each cycle is calculated by applying the appropriate risk of discontinuation directly to the number of patients in each health state at each cycle:

$n_{disc\ i} = n_{on\ tmt\ cy\ i} \times r_i$, where:

- i is the cycle under consideration.
- r_i is the risk of discontinuation for cycle i.
- $n_{on\ tmt\ cy\ i}$ is the number of patients on treatment at the beginning of cycle i.
- $n_{disc\ i}$ is the number of patients who discontinue in cycle i.

In subsequent cycles, cumulative numbers of patients who had discontinued in prior cycle were estimated, while accounting for those who had left the health state because of relapse or death.

Mortality

The risk is applied to the number of patients alive at the beginning of the cycle in each health state: $n_{death\ cycle\ i} = n_{alive\ cycle\ i} \times p_{death}$, where:

- i is the cycle under consideration
- $n_{death\ cycle\ i}$ is the number of patients that die during cycle i
- $n_{alive\ cycle\ i}$ is the number of patients alive at the beginning of cycle i
- $p_{death} = 1 - e^{[Ln(1-p_{age}-p_{suicide})]}$ is the combined all-cause and suicide mortality risk
- p_{age} is the all-cause mortality risk at a given age
- $p_{suicide}$ is the suicide-related mortality risk

At the beginning of the model, the mortality risk for the baseline age of the cohort (also a user input) is used. For example, if the model starting age is 46 years, the all-cause mortality risk during Year 1 would be that of a 46-year old from the weighted all-cause mortality risk table; during Year 2 it would be that of a 47-year old, and so on.

The additional mortality from suicide is also explicitly modeled and is added on top of the all-cause mortality.

AE-associated Utility Decrement Calculations

For each AE included in the model, treatment-dependent inputs are used to calculate the associated utility decrement by treatment: the incidence for each AE by treatment, the duration of each event, and

the utility decrement of each event. The utility decrement for each AE is determined by calculating the product of the disutility, incidence, and duration of the event: $U_{tx} = U_{AE} \times I \times Dur$, where:

- U_{tx} is the utility decrement for each specific AE by treatment
- U_{AE} are the utility decrements of the AE
- I is the incidence of the AE by treatment per cycle
- Dur is the duration of the AE

10 Appendix B

Limitations of TRANSFORM-2 to inform the relative effect of esketamine nasal spray

The esketamine nasal spray phase III clinical trials are placebo-controlled (placebo nasal spray), however the comparator arm includes an active treatment as patients are also prescribed new SSRI/SNRI (i.e. an oral drug that has not been previously prescribed). This active comparator arm is unlikely to reflect the true treatment effect of a newly initiated oral AD seen in clinical practice, as patients received intense healthcare professional contact for the nasal spray administration. This was to ensure double-blinding of the randomised clinical trial; however, it clearly differs from clinical practice.

The active comparator arm of the TRANSFORM-2 trial is very different from the active comparator arms in other antidepressant trials. The systematic literature review of clinical trials in TRD (performed to inform the health economic analysis) showed there is no other trial conducted with a similarly high number of follow-up visits (eight visits in four weeks) and the use of nasal spray in the active comparator arm. The presence of these aspects is known to contribute to a therapeutic response. It has been shown that follow-up visit assessments in oral AD treatment trials translate into a significant therapeutic effect, representing about 40% of the placebo response (Posternak, Zimmerman 2007).(26)

Additionally, a clinical trial setting can increase the patient expectations in the active comparator arm. In the esketamine nasal spray trials there are cases of patients given the placebo nasal spray who reported the adverse event of dissociation, which should be unique to the active ingredient of esketamine.

The response rate (≥50% reduction in MADRS) in TRANSFORM-2 for the placebo nasal spray plus oral AD group was considerably higher than expected based on those reported in the STAR*D trial. STAR*D is the largest and most comprehensive study on oral ADs ever conducted and was a prospective, sequentially randomized controlled trial of outpatients with nonpsychotic major depressive disorder. Patients received one (n=3,671) to four (n=123) successive acute treatment steps, including treatment combinations and augmented therapies where step 3 and 4 (two or three previous AD treatment failures) are applicable to the TRD population. In STAR*D the response rate was 13.7% (≥50% reduction in QIDS-SR) compared with a response rate of 52% in the TRANSFORM-2 placebo nasal spray plus oral AD arm. This is in a similar population of treatment resistant depression (with two previous AD failures i.e. treatment step 3 in STAR*D), however the mean treatment duration differed markedly with STAR*D of 8.6 weeks (SD: 5.2 weeks) (Rush et al, 2006) and TRANSFORM-2 of 28 days (primary endpoint).

In a systematic literature review identified two other trials with SSRI/SNRI in the TRD population, see table Ab1. A naïve comparison of the trials indicates that the results from the placebo nasal spray plus oral AD arm observed in TRANSFORM-2 are high.

Table Ab1: Comparison of SSRI/SNRI trials in a TRD population with data from TRANSFORM-2 (change in MADRS score from baseline to 4 weeks)

	Randomised treatment regimen	Endpoint, weeks	Change from baseline MADRS score
Corya, 2006	• Switch fluoxetine 25 or 50mg/day	4	-6.92
Shelton, 2005	• Switch fluoxetine 25-50 mg/day	4	-6.84 [0.38]
TRANSFORM-2	• Switch SSRI (escitalopram or sertraline) or SNRI (duloxetine or venlafaxine XR) according to local prescribing guidelines (open label) • Placebo nasal spray twice weekly	4	-16.3 (14.24)

11 Appendix C

Proportion of patient of moderate to severe TRD patients, proportion receiving SSRI or SNRI as first treatment after TRD diagnosis and concomitant use

Table Ac1 displays treatment shift within one year **after** fulfillment of the TRD definition stratified on disease severity. TRD-DT0 is the treatment where the patients comply with the TRD definition. Out of the 29.210 TRD patients identified, 17.428 have moderate to severe TRD corresponding to approx. 60%. Furthermore, 13.659 out of the 17.428 patients received SSRI or SNRI as their first treatment after TRD diagnosis, corresponding to approx. 80%.

Table Ac1 also illustrates the current concomitant use of anti-psychotics together with a SSRI or SSRI as first line therapies. As the table illustrates less than 1% is receiving concomitant anti-psychotic treatment.

Table Ac1. First treatment after TRD diagnosis meaning that the patients have failed two antidepressants

		Concomitant use		
TRD-DT0	Total (TRD-DT0)	*Psycho-therapy*	*Lithium*	*Anti-psychotics*
SSRI				
Mild	3.787	9	<5	10
	13%	0%	0%	0%
Moderate	3.088	<5	<5	5
	11%	0%	0%	0%
Severe	1.420	<5	<5	<5
	5%	0%	0%	0%
SNRI				
Mild	6.253	<5	<5	6
	21%	0%	0%	0%
Moderate	6.150	6	<5	<5
	21%	0%	0%	0%
Severe	3.001	<5	<5	<5
	10%	0%	0%	0%
TCA				
Mild	1.467	<5	<5	<5
	5%	0%	0%	0%
Moderate	1.529	<5	<5	<5
	5%	0%	0%	0%
Severe	1.276	<5	<5	<5
	4%	0%	0%	0%
MAOI				

		Concomitant use		
Mild	28	<5	<5	<5
	0%	0%	0%	0%
Moderate	34	<5	<5	<5
	0%	0%	0%	0%
Severe	14	<5	<5	<5
	0%	0%	0%	0%
ECT				
Mild	249	<5	<5	<5
	1%	0%	0%	0%
Moderate	332	<5	<5	<5
	1%	0%	0%	0%
Severe	584	<5	<5	<5
	2%	0%	0%	0%

*Please note that 2 patients are not included in this analysis

Proportion of patient of moderate to severe TRD patients receiving concomitant use of anti-psychotics together with the second treatment after TRD diagnosis

Table Ac2 displays TRD-DT+1 which is equivalent to the second treatment after TRD diagnosis (the fourth consecutive alteration of the overall depression treatment of the patient). Furthermore, the table shows the concomitant use of anti-psychotics together with SSRI and SNRI as second treatment after TRD diagnosis for moderate to severe TRD patients. The weighted use of anti-psychotics was calculated to be 10.5% by analyzing the moderate and severe patients highlighted with bold typing in table Ac2. The total number of TRD-DT+1 patients with moderate to severe TRD receiving a SSRI or SNRI is 5.261.

The calculation of the weighted use of anti-psychotics:

(126/859)*(859/5.261)+(108/466)*(466/5.261)+(181/2.342)*(2342/5.261)*(139/1.594)*(1.594/5.261)= 10.5%

Table Ac2. Second treatment after TRD diagnosis meaning that the patients have failed 3 antidepressants.

		Concomitant use		
TRD-DT+1	Total (TRD-DT+1)	*Psycho therapy*	*Lithium*	*Anti psychotics*
SSRI				
Mild	936	<5	<5	168
	3%	0%	0%	18%
Moderate	**859**	<5	<5	**126**
	3%	0%	0%	**15%**
Severe	**466**	<5	<5	**108**
	2%	0%	0%	**23%**

			Concomitant use	
SNRI				
Mild	2.438	<5	<5	189
	8%	0%	0%	8%
Moderate	**2.342**	<5	<5	**181**
	8%	0%	0%	**8%**
Severe	**1.594**	<5	<5	**139**
	5%	0%	0%	9%
TCA				
Mild	656	<5	<5	63
	2%	0%	0%	10%
Moderate	719	<5	<5	55
	2%	0%	0%	8%
Severe	539	<5	<5	76
	2%	0%	0%	14%
MAOI				
Mild	28	<5	<5	<5
	0%	0%	0%	0%
Moderate	25	<5	<5	<5
	0%	0%	0%	0%
Severe	18	<5	<5	<5
	0%	0%	0%	0%
ECT				
Mild	90	<5	<5	<5
	0%	0%	0%	0%
Moderate	106	<5	<5	<5
	0%	0%	0%	0%
Severe	123	<5	<5	<5
	0%	0%	0%	0%
No second				
Mild	7.636	*n/a*	*n/a*	*n/a*
	26%			
Moderate	7.082	*n/a*	*n/a*	*n/a*
	24%			
Severe	3.555	*n/a*	*n/a*	*n/a*
	12%			

Population projection and eligible TRD patients for treatment with Spravato in combination with a SSRI or SNRI in the period 2021-2025

For the full TRD population (clinical question 1) there are 6.170 patients with moderate to severe TRD and receiving a SSRI or SNRI which are eligible for treatment with Spravato in 2021, see table Ac3. The eligible patients in the following years were projected by dividing the eligible number of patients in 2021 with the number of adults in the Danish population in 2021 and then multiplying with the number of adults in 2022 with the increase of adults in the Danish population.

Example of the calculation for 2022:

- 6.170/4.687.000*4.708.300 = 6.918

Furthermore the estimated number of adults in the Danish population at each year derived from Statistics Denmark´s population projection.

Table Ac3: Projection of patients in the full TRD population (clinical question 1) receiving a SSRI or SNRI which are eligible for treatment with Spravato in the period 2021-2025

Year	2021	2022	2023	2024	2025
Adults in the Danish population	4.687.000	4.708.300	4.735.400	4.760.500	4.785.000
Eligible TRD patients – full TRD population (clinical question 1)	6170	6198	6234	6267	6299

For the full MSM ≥ 9 subpopulation (clinical question 2) we assume that there are 1.000 patients which are eligible for treatment with Spravato each year, see table Ac4. This assumption is based on the Scientific Committee stating: "a small proportion of patients who have tried several treatment alternatives without success can try treatment with esketamine. This estimate is approx. 1000 patients." This statement is available at page 34 in the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1.(61)

Table Ac4: Patients in the MSM ≥ 9 subpopulation (clinical question 2) which are eligible for treatment with Spravato in the period 2021-2025

Year	2021	2022	2023	2024	2025
Adults in the Danish population	4.687.000	4.708.300	4.735.400	4.760.500	4.785.000
Eligible TRD patients – MSM ≥ 9 subpopulation (clinical question 2)	1000	1000	1000	1000	1000

12 Appendix D

We acknowledge the Expert Committee had concerns around the base case model specifically related to the lack of function to include retreatment in the model. We firmly believe, however, that including assumptions to inform retreatment brings additional uncertainty due to the lack of data to inform the analysis. Including retreatment is also inconsistent with previous HTA evaluation of treatments for depression in other countries i.e. NICE decision making in NICE TA 367 *[vortioxetine for treating major depressive episodes*] and NICE CG 90 *[Depression in adults: recognition and management],* where it has not been considered. Furthermore, NICE made the following statement regarding a similar retreatment model that was provided in UK for the evaluation of esketamine:

"The committee acknowledged that there were no data to inform outcomes for people who have repeat treatment. It recognized that the company's preference to model 1 line of esketamine treatment may be the most informative, despite the committee's preference for a longer time horizon. The committee concluded that the company's approach of modelling repeat treatment was not appropriate with the current evidence."

Regardless, as a retreatment model was explicitly requested by the Medicines Council and Expert Committee, we have provided scenarios to show the impact of retreatment on the incremental cost and cost-effectiveness of ESK-NS. The scenarios show that retreatment improves both the incremental cost and the cost-effectiveness of ESK-NS.

12.1 Limitations of the retreatment model

As noted above, incorporating retreatment increases uncertainty in the analysis. The retreatment option is incorporated in the previously submitted Markov model, which comes with a number of restrictions inherent with a Markov model. Further discussion of the limitations are below:

- In the retreatment model scenario, retreatment is only for patients treated with ESK-NS + OAD who had previously been in stable remission for at least 9 months, then discontinued ESK-NS, and subsequently experienced a recurrence while in the recovery health state.
- The positioning and sequencing of ESK-NS during retreatment of the new episode is uncertain and based on assumptions, since there are many factors that affecting whether a patient will be retreated with ESK-NS in Danish clinical practice, of which access to health care professionals is key.
- The data to inform the effectiveness of ESK-NS during retreatment are based on the assumptions taken from initial treatment of the first episode with ESK-NS.
- It is assumed similar health states (MDE, remission and recovery (but no response)) also apply to ESK-NS in retreatment of the new episode.
- The data to inform relapse and recurrence for ESK-NS are based upon assumptions taken from the initial treatment with ESK-NS.
- The dosage and frequency of ESK-NS (and hence treatment costs) are based upon initial ESK-NS treatment.

- The safety profile of ESK-NS retreatment is assumed to be consistent with initial treatment with ESK-NS.
- The proposed approach assumes that every episode of depression after an episode of TRD will be treatment-resistant and patients will receive ESK-NS retreatment in the absence of data.

Overall, the retreatment scenario significantly increases the uncertainty in the incremental cost and cost-effectiveness of ESK-NS. The above limitations show that the retreatment model should not be considered more than a scenario and should be interpreted with caution.

Conclusion: Given the uncertainty associated with the retreatment model, the existing company base case model is the most robust to base decision making on for ESK-NS

12.1.1 New scenarios incorporating retreatment improves the cost effectiveness of ESK-NS

Given the Medicines Council and Expert Committee's explicit request and despite our reservations highlighted above, we have developed a model which attempts to incorporate retreatment, presented below.

It is important to note that based upon clinical opinion and the Expert Committee´s request, retreatment will only be used in clinical practice if the active treatment was successful before, and the patient is no longer on that treatment, i.e. patients who have been in stable remission for at least 9 months and have discontinued ESK-NS will be eligible for ESK-NS retreatment. This is aligned to the modelling approach that we have taken in this exploratory scenario which also aligns the Expert Committees statement in the initial evaluation of esketamine for TRD:

"Fagudvalget vurderer, at hvis esketamin + OA har haft effekt på en patient, og patienten får en ny episode, ville esketamin kunne gives igen. Fagudvalget vurderer dog, at patienten i sin levetid sammenlagt højst vil modtage esketamin i 1-2 år"

The statement is available in the background document for the Medicines Councils recommendation of esketamine for the treatment of TRD in adults, version 1. (61)

The exploratory retreatment scenarios for the full TRD, MSM ≥ 7, MSM ≥ 8 and MSM ≥ 9 populations show that including repeat courses of ESK-NS treatment for patients who discontinue in recovery but subsequently have a recurrence improves the incremental cost and cost-effectiveness of ESK-NS. This is because recurrence (transition from recovery to the active MDE health state), increases the proportion of patients subsequently entering remission compared to the original model. In the original model, patients who had a recurrence moved to a subsequent treatment rather than being re-treated with ESK-NS. The increased proportion of patients entering remission reflects the additional clinical benefit of ESK-NS retreatment compared to the subsequent therapies. Keeping more patients in the remission health state significantly reduces the disease management costs, which offsets the additional drug and administration costs of ESK-NS re-treatment.

The CUA results for the full TRD and the MSM ≥ 9 subpopulation are available in sections 12.2 and 12.3, respectively. Furthermore, the budget impact results based on the retreatment model are available in section 12.4 and 12.5 for the full TRD population and the MSM ≥ 9 subpopulation, respectively.

12.2 Scenario CUA Results for the full TRD population (clinical question 1)

12.2.1 Retreatment model results

The retreatment model clinical and economic outcomes for the full TRD population (clinical question 1) are presented in Table Ad1 and Ad2. Over a five-year time horizon, esketamine nasal spray plus oral AD was associated with additional 0.540 QALYs compared with oral AD. The incremental cost for esketamine nasal spray plus oral AD in the retreatment scenario with restricted societal perspective was DKK 32.427 for the full TRD population (clinical question 1). However, over the five-year time horizon, esketamine nasal spray plus oral AD was estimated to have lower disease management costs, in particular saving DKK 51.590 compared with oral AD and also lower administration cost, saving DKK 22.798. When including productivity loss the incremental cost for esketamine nasal spray plus oral AD was DKK 191.190 and when looking separately at the Indirect costs for esketamine nasal spray plus oral AD, it was DKK 223.617 lower compared with oral AD.

Table Ad1. Effectiveness Outcomes (Discounted) for the full TRD population (clinical question 1)

Health State	ESK + Oral AD	Oral AD	Difference
Total life years	**4,525**	**4,513**	**0,012**
MDE	2,612	3,581	-0,970
Response	0,221	0,296	-0,074
Remission	0,701	0,394	0,307
Recovery	0,991	0,242	0,749
Total QALYs	**2,739**	**2,198**	**0,540**
MDE	0,998	1,368	-0,370
Response	0,183	0,244	-0,061
Remission	0,645	0,363	0,282
Recovery	0,913	0,223	0,690
AE	0,000	0,000	0,000

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode

Table Ad2. Cost Outcomes (Discounted) for the full TRD population (clinical question 1)

Cost Outcomes	ESK + Oral AD	Oral AD	Difference
BASE CASE RESULTS			
Total costs	**DKK 548.133**	**DKK 515.706**	**DKK 32.427**
Treatment Acquisition	DKK 110.100	DKK 3.325	DKK 106.775
Treatment Administration and Monitoring	DKK 260.059	DKK 282.857	-DKK 22.798

Cost Outcomes	ESK + Oral AD	Oral AD	Difference
Disease Management	DKK 177.926	DKK 229.517	-DKK 51.590
AE Management	DKK 47	DKK 7	DKK 40
INDIRECT COST RESULTS			
Productivity Loss	DKK 1.021.996	DKK 1.245.614	-DKK 223.617

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; RW = real-world

Furthermore, esketamine nasal spray plus oral AD yielded greater clinical benefits, which translated into higher QALYs and savings, in disease management costs compared with oral AD. Table Ad3 shows the incremental cost-effectiveness outcomes. Esketamine nasal spray plus oral AD resulted in cost savings and higher QALYs compared with oral AD from the societal perspective (esketamine nasal spray plus oral AD was dominant).

Table Ad3. Incremental Cost Effectiveness Outcomes for the full TRD population (clinical question 1)

Outcomes	ESK + Oral AD vs. Oral AD
BASE CASE RESULTS	
Incremental QALYs	0,540
Incremental costs, restricted societal perspective	DKK 32.427
ICER—cost per QALY gained, restricted societal perspective	DKK 60.013
INDIRECT COST RESULTS	
Incremental costs, societal perspective	-DKK 191.190
ICER—cost per QALY gained, societal perspective	-DKK 353.839

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RW = real-world

12.3 Scenario CUA Results for the MSM ≥ 9 subpopulation (clinical question 2)

12.3.1 Retreatment model results

The base case clinical and economic outcomes for the MSM ≥ 9 subpopulation (clinical question 2) are presented in Table Ad4 and Table Ad5. Over a five-year time horizon, esketamine nasal spray plus oral AD was associated with additional 0.675 QALYs compared with oral AD. The incremental cost for esketamine nasal spray plus oral AD in the retreatment scenario with restricted societal perspective was DKK 10.948 for the MSM ≥ 9 subpopulation (clinical question 2). However, over the five-year time horizon, esketamine nasal spray plus oral AD was estimated to have lower disease management costs, in particular saving DKK 78.251 compared with oral AD and also lower administration cost saving DKK 18.434.

When including productivity loss the incremental cost for esketamine nasal spray plus oral AD was DKK -263.380 and when looking separately at the indirect costs for esketamine nasal spray plus oral AD it was DKK 274.328 lower compared with oral AD.

Table Ad4. Effectiveness Outcomes (Discounted) for the MSM ≥ 9 subpopulation (clinical question 2)

Health State	ESK + Oral AD	Oral AD	Difference
Total life years	**4,524**	**4,508**	**0,016**
MDE	2,705	3,911	-1,207
Response	0,234	0,296	-0,062
Remission	0,660	0,288	0,372
Recovery	0,925	0,012	0,913
Total QALYs	**2,708**	**2,033**	**0,675**
MDE	1,036	1,498	-0,462
Response	0,203	0,257	-0,054
Remission	0,611	0,267	0,344
Recovery	0,858	0,011	0,846
AE	0,000	0,000	0,000

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; MDE = major depressive episode

Table Ad5. Cost Outcomes (Discounted) for the MSM ≥ 9 subpopulation (clinical question 2)

Cost Outcomes	ESK + Oral AD	Oral AD	Difference
BASE CASE RESULTS			
Total costs	**DKK 600.910**	**DKK 589.962**	**DKK 10.948**
Treatment Acquisition	DKK 110.914	DKK 3.322	DKK 107.592
Treatment Administration and Monitoring	DKK 264.107	DKK 282.541	-DKK 18.434
Disease Management	DKK 225.843	DKK 304.093	-DKK 78.251
AE Management	DKK 47	DKK 7	DKK 40
INDIRECT COST RESULTS			
Productivity Loss	DKK 1.044.236	DKK 1.318.564	-DKK 274.328

Abbreviation: AD = antidepressant; AE = adverse event; ESK = esketamine; RW = real-world

Furthermore, esketamine nasal spray plus oral AD yielded greater clinical benefits, which translated into higher QALYs and savings, in disease management costs compared with oral AD. Table Ad6 shows the incremental cost-effectiveness outcomes. Esketamine nasal spray plus oral AD resulted in cost savings and higher QALYs compared with oral AD from the societal perspective (esketamine nasal spray plus oral AD was dominant).

Table Ad6. Incremental Cost Effectiveness Outcomes for the MSM ≥ 9 subpopulation (clinical question 2)

Outcomes	ESK + Oral AD vs. Oral AD
BASE CASE RESULTS	
Incremental QALYs	0,675
Incremental costs, restricted societal perspective	DKK 10.948
ICER—cost per QALY gained, restricted societal perspective	DKK 16.228
INDIRECT COST RESULTS	
Incremental costs, societal perspective	-DKK 263.380
ICER—cost per QALY gained, societal perspective	-DKK 390.394

Abbreviation: AD = antidepressant; ESK = esketamine; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RW = real-world

12.4 Budget impact results for the full TRD population (clinical question 1)

12.4.1Retreatment model results

The results of the retreatment scenario budget impact analysis for the full TRD population (clinical question 1) with the introduction of Spravato® in combination with a SSRI or SNRI is shown in Table Ad7 and the budget impact including indirect cost is shown in table Ad8.

The adoption of Spravato®, in combination with a SSRI or SNRI, as standard treatment to the market is associated with a slight increase in resource use for the treatment of TRD patients who currently do not have an effective and approved standard treatment.

- The result can be found in the sheet "Budget impact – base case" in the excel model. It is worth noting that the inclusion of patients needs to be set at 0% in the "Settings" sheet and then the model should be run.

Table Ad7: Base case results for the budget impact analysis for the full TRD population (clinical question 1)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	DKK 13.840.126	DKK 27.805.868	DKK 38.455.139	DKK 49.201.986	DKK 56.517.962
Drug	DKK 27.239.715	DKK 54.726.662	DKK 75.686.232	DKK 96.837.849	DKK 111.236.930
Administration	DKK 402.035	DKK 807.719	DKK 1.117.064	DKK 1.429.244	DKK 1.641.762
Medical costs	-DKK 13.811.575	-DKK 27.748.507	-DKK 38.375.809	-DKK 49.100.486	-DKK 56.401.369
AEs	DKK 9.952	DKK 19.993	DKK 27.651	DKK 35.378	DKK 40.638
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

Thus, the recommendation of Spravato® in combination with a SSRI or SNRI as standard treatment for the full TRD population (clinical question 1), consisting of adults with moderate to severe TRD who have failed on at least two antidepressants, will give patients the possibility to get a new innovative treatment which provides fast and increased response, remission and improved quality of life which will translate into improvement in patient social and occupational functioning. Furthermore, this will have a positive impact on not only the patients themselves, but also their family, friends, and carers. In addition, the budgetary expenses in the regions related to hospitalization will decrease.

Furthermore, the introduction of Spravato will lower the societal financial expenditure associated with treatment of TRD patient in full TRD population, if indirect cost are taking into consideration, as shown in table Ad8.

Table Ad8: Results for the budget impact analysis including indirect costs for treatment of the full TRD population (clinical question 1)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-DKK 46.021.848	-DKK 92.461.399	-DKK 127.872.862	-DKK 163.608.790	-DKK 187.936.222
Drug	DKK 27.239.715	DKK 54.726.662	DKK 75.686.232	DKK 96.837.849	DKK 111.236.930
Administration	DKK 402.035	DKK 807.719	DKK 1.117.064	DKK 1.429.244	DKK 1.641.762
Medical costs	-DKK 13.811.575	-DKK 27.748.507	-DKK 38.375.809	-DKK 49.100.486	-DKK 56.401.369
AEs	DKK 9.952	DKK 19.993	DKK 27.651	DKK 35.378	DKK 40.638
Indirect costs to patients	-DKK 59.861.975	-DKK 120.267.267	-DKK 166.328.001	-DKK 212.810.775	-DKK 244.454.184
Indirect costs to caregivers	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

12.5Budget impact results for the MSM ≥ 9 subpopulation (clinical question 2)

12.5.1Retreatment model results

The results of the retreatment scenario budget impact analysis for the MSM ≥ 9 subpopulation (clinical question 2) with the introduction of Spravato® in combination with a SSRI or SNRI, is shown in Table Ad9 and the budget impact including indirect cost is shown in table Ad10.

The adoption of Spravato®, in combination with a SSRI or SNRI, as standard treatment to the market is associated with a slight increase in resource use for the treatment of TRD patients with a MSM ≥ 9 score who currently do not have an effective and approved standard treatment.

- The result can be found in the sheet "Budget impact – base case" in the excel model. It is worth noting that the inclusion of patients needs to be set at 0% in the "Settings" sheet and then the model should be run.

Table Ad9: Base case results for the budget impact analysis for the MSM ≥ 9 subpopulation (clinical question 2)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	DKK 7.239.355	DKK 14.537.327	DKK 20.106.062	DKK 25.704.105	DKK 29.309.128
Drug	DKK 27.373.955	DKK 54.969.562	DKK 76.026.451	DKK 97.194.165	DKK 110.825.730
Administration	DKK 651.590	DKK 1.308.455	DKK 1.809.678	DKK 2.313.538	DKK 2.638.014
Medical costs	-DKK 20.796.150	-DKK 41.760.690	-DKK 57.757.728	-DKK 73.838.962	-DKK 84.194.939
AEs	DKK 9.960	DKK 20.000	DKK 27.661	DKK 35.363	DKK 40.322
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

Thus, the recommendation of Spravato® in combination with a SSRI or SNRI as standard treatment for the MSM ≥ 9 subpopulation (clinical question 2), will give patients the possibility to get a new innovative treatment which provides fast and increased response, remission and improved quality of life which will translate into improvement in patient social and occupational functioning. Furthermore, this will have a positive impact on not only the patients themselves, but also their family, friends, and carers. In addition, the budgetary expenses in the regions related to hospitalization will decrease.

In addition, the introduction of Spravato will lower the societal financial expenditure associated with treatment of TRD patient in MSM ≥ 9 subpopulation, if indirect costs are taking into consideration, as shown in table Ad10.

Table Ad10: Results for the budget impact analysis including indirect costs for treatment of the MSM ≥ 9 subpopulation (clinical question 2)

Adoption	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
Total Net Cost per Year	-DKK 65.670.255	-DKK 131.872.252	-DKK 182.387.833	-DKK 233.169.285	-DKK 265.871.476
Drug	DKK 27.373.955	DKK 54.969.562	DKK 76.026.451	DKK 97.194.165	DKK 110.825.730
Administration	DKK 651.590	DKK 1.308.455	DKK 1.809.678	DKK 2.313.538	DKK 2.638.014
Medical costs	-DKK 20.796.150	-DKK 41.760.690	-DKK 57.757.728	-DKK 73.838.962	-DKK 84.194.939
AEs	DKK 9.960	DKK 20.000	DKK 27.661	DKK 35.363	DKK 40.322
Indirect costs to patients	-DKK 72.909.609	-DKK 146.409.580	-DKK 202.493.894	-DKK 258.873.390	-DKK 295.180.604
Indirect costs to caregivers	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Relapse costs	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0

Medicinrådet

Medicinrådets protokol for revurdering vedrørende esketamin til behandling af behandlingsresistent depression hos voksne

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel Medicinrådet undersøger, den behandling Medicinrådet sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

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1. Begreber og forkortelser

EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HDRS	*Hamilton Depression Rating Scale*
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
ICD-10	*International Classification of Diseases and Related Health Problems-10*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention to treat*
MADRS:	*Montgomery-Åsberg Depression Rating Scale*
MDD:	*Major Depressive Disorder*
MKRF:	Mindste klinisk relevante forskel
MSM:	*Maudsley Staging Method*
NaSSA:	Hæmmere af adrenerge receptorer
NICE:	*The National Institute for Health and Care Excellence*
NMDA:	N-methyl-D-aspartat
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RADS:	Rådet for Anvendelse af Dyr Sygehusmedicin
RR:	Relativ risiko
SNRI:	Serotonin-/noradrenalingenoptagelseshæmmer
SSRI:	Serotoningenoptagshæmmer
SMD:	*Standardized Mean Difference*

TCA: Tricykliske antidepressiva

2. Introduktion

Medicinrådet har tidligere i 2020 vurderet esketamin (Spravato) til behandlingsresistent depression. Denne protokol er udarbejdet, fordi Medicinrådet har modtaget en ny foreløbig ansøgning fra Janssen-Cilag, som ønsker, at Medicinrådet revurderer esketamin i kombination med et SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode. Baggrunden er fremkomsten af nye data. Medicinrådet modtog den foreløbige ansøgning den 18. december 2020. Janssen Cilag fik markedsføringstilladelse i EU den 18. december 2019.

2.1 Moderat til svær unipolar depression hos voksne

Moderat til svær unipolar depression, eller Major Depressive Disorder (MDD), vil ifølge WHO inden for en tidsramme af 20 år være blandt de to mest belastende sygdomme i verden, hvad angår sygdomsbyrde og økonomiske konsekvenser for samfundet. I Danmark anslås prævalensen af moderat til svær depression blandt voksne at være ca. 3 % svarende til ca. 111.000 voksne individer [1,2]. Det skønnes, at kun 65,3 % af disse, svarende til ca. 72.400 voksne individer, bliver diagnosticeret og kan komme i behandling [2]. Ca. 14 %, svarende til ca. 10.100 voksne individer, har ikke en tilfredsstillende effekt af behandlingen [2,3] og er mulige kandidater til behandling med intranasal esketamin. En mindre andel af disse vil dog i praksis ikke blive tilbudt behandlingen, fordi de er særligt sårbare (typisk ved høj alder i kombination med somatisk komorbiditet) eller pga. misbrug, psykiatrisk- eller somatisk komorbiditet i øvrigt.

Depression viser sig på mange måder, men præsenterer sig typisk med symptomer som en følelse af at være trist og træt over længere tid, manglende selvværd, isolationstendens, selvbebrejdelser, nedsat eller øget appetit, tab af livslyst og måske selvmordstanker eller -planer [4]. I alvorlige tilfælde kan der være psykotiske symptomer i form af hallucinationer og vrangforestillinger [4].

Depression inddeles i mild, moderat og svær depression. Patienter med svær depression har en overhyppighed af selvmord, og tilbagefald er hyppige og forekommer med stigende frekvens afhængigt af, hvor mange depressioner man tidligere har haft [5]. Nogle får kronisk depression, hvor de depressive symptomer fortsætter igennem flere år [4]. Depression ses ofte sammen med andre psykiske lidelser som f.eks. angst og personlighedsforstyrrelser og kan optræde parallelt til alvorlige fysiske lidelser som f.eks. diabetes, kræft og hjertesygdom [4]. Herudover er misbrugsproblemer også almindeligt hos patienter med svær depression [4].

Depression kan udløses af længerevarende somatisk sygdom, stress, tab af nærtstående og eksistentielle kriser, men ofte er de udløsende faktorer ukendte. Genetisk prædisposition og personlighedsmæssige disponerende forhold bidrager til at øge risikoen for sygdommen [4]. Den nuværende medicinske behandling virker bl.a. ved at regulere signalstofferne serotonin og noradrenalin i hjernen. En stigende mængde evidens

indikerer desuden, at dysregulering af glutamatsignaleringen i hjernen også kan være involveret i depression [6].

Nogle patienter responderer ikke på den nuværende medicinske behandling og beskrives som havende behandlingsresistent depression. Definitionen af denne population er varierende. Ifølge Sundhedsstyrelsen omfatter behandlingsresistent depression voksne patienter over 18 år (både ambulante og indlagte) med moderat til svær depression, diagnosticeret efter ICD-10 (WHO's diagnoseliste) kriterier eller er vurderet behandlingsresistent på *Rating Scale for Treatment-Resistant Depression*, f.eks. ***Maudsley Staging Method*** (MSM) [7,8].

Hvis patienten med depression tidligere har haft maniske eller hypomane episoder, betegnes depressionen som en bipolar depression, der er led i en bipolar lidelse. En andel af patienterne med behandlingsresistent depression vil have en ikkediagnosticeret bipolar depression, hvor de senere i forløbet vil udvikle mani eller hypomani [5,9].

2.2 Esketamin

Esketamin, eller s-ketamin, er ét af to spejlmolekyler af ketamin (s- og r-ketamin). Brugen af s-ketamin fremfor r-ketamin forventes at øge specificiteten og derved mindske bivirkninger ved brug [10]. Esketamin udøver sin effekt i hjernen via N-methyl-D-aspartat (NMDA)-receptoren, der er et modtagermolekyle for glutamat. Glutamat frigives normalvis som et signalmolekyle i kontaktfladen mellem nerveceller i hjernen. Esketamin leder til en forbigående forøgelse i frigivelsen af glutamat, som trinvist fører til en forøgelse i neurotrofisk signalering, der er essentiel for nervecellernes funktion og overlevelse [6,11,12]. Dette antages at bidrage til at genoprette funktionen i hjerneområder involveret i reguleringen af affektiv og emotionel adfærd [6,11,12]. Esketamin, som ketamin, har dissociative effekter, der typisk efterlader brugeren med en følelse af at forlade kroppen [10]. Andre psykotomimetiske effekter er også beskrevet.

Til behandlingen af behandlingsresistent depression hos voksne er esketamin udviklet som en nasal formulering [2]. Den intranasale administrationsvej er forbundet med en hurtig indsættende effekt, hvor det kan tage flere uger at opnå en ønsket effekt med de traditionelt anvendte orale antidepressiva [2]. Esketamin har været administreret i kliniske forsøg som monoterapi og som add-on terapi med antidepressiva [13–15]. Behandlingen omfatter en induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg eller 56 mg (afhængigt af alder, effektivitet og tolerabilitet) nasal esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling [2]. Efter induktionsfasen følger en vedligeholdelsesbehandling med nasal esketamin 56 mg eller 84 mg én gang ugentlig fra uge 5-8 og herefter hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen [2]. Hvornår/om, behandlingen kan eller skal stoppes, er endnu uafklaret.

2.3 Nuværende behandling

En af de største barrierer for forståelsen af behandlingsresistent depression er den manglende konsensus omkring definition og diagnosticering. Ifølge fagudvalget favner den hyppigst anvendte definition, bestemt efter ICD-10-kriterier, meget bredt, idet den omfatter patienter, som ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og i tilstrækkelig lang tid (≥ 4 uger) eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling. Risikoen ved at anvende disse kriterier er, at patienter diagnosticeres som behandlingsrefraktære for tidligt, dvs. før de er blevet tilbudt andre tilgængelige præparater eller behandlinger inkl. ikkemedicinske alternativer. En anden metode til at definere behandlingsresistent depression, som vinder indpas internationalt, er spørgeskemaet MSM [7]. MSM er udviklet med henblik på at definere behandlingsresistens ved unipolar depression og anses for at have mere stringente kriterier end ICD-10, hvor det tilmed er muligt at inddele sværhedsgraden af behandlingsresistent depression. Den maksimale score for MSM er 15, og scoren er kategoriseret i mild: 3-6, moderat: 7-10 og svær 11-15 [7].

Behandlingen af behandlingsresistent depression er ikke defineret i den gældende behandlingsvejledning for medicinsk behandling af unipolær depression udarbejdet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) i 2015. En national klinisk retningslinje vedrørende vanskelig behandlelig depression er under udarbejdelse af en arbejdsgruppe under Sundhedsstyrelsen. I henhold til RADS' vejledning bør behandlingen af patienter med moderat til svær depression tilgås som følgende: Den indledende behandling af ikkehospitaliserede patienter skal bestå af SSRI som førstelinjebehandling, der gives over 1-3 måneder. En fuld effekt af antidepressiva kan først ventes efter 4-6 uger. Opnår patienten en tilfredsstillende effekt ved behandlingen, fortsættes i en vedligeholdelsesfase i ca. 6-12 måneder eller længere, afhængigt af kliniske forhold. Hvis der ikke er tegn på bedring efter ca. 2-4 uger på optimal dosis (i praksis ofte længere), skiftes der til andenlinjebehandling, som består af enten SSRI, SNRI, hæmmere af adrenerge receptorer (NaSSA) eller tricykliske antidepressiva (TCA). Er der fortsat ikke tegn på bedring, henvises der til psykiater eller indlæggelse på psykiatrisk afdeling. Blandt indlagte/hospitaliserede patienter med svær depression skal overvejes start med SNRI eller TCA.

Dansk registerdata viser, at SSRI og SNRI er de hyppigst anvendte tredjelinjebehandlinger i Danmark [3].

Behandlingsvarigheden varierer fra patient til patient. Til patienter, der er refraktære overfor behandling med antidepressiva, overvejes en række alternativer til medicinsk behandling. Disse inkluderer: psykoterapi, elektrochok og i særlige tilfælde magnetstimulation.

Målet med behandling af behandlingsresistent depression er at opnå remission af depressive symptomer, øge livskvaliteten og forhindre selvmord blandt en patientgruppe med øget selvmordstendens.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med behandlingsresistent depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva i den aktuelle moderate til svære depressive episode?

Population
Patienter over 18 år med behandlingsresistent depression bestemt som patienter, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger), eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling.

Intervention
Induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg* eller 56 mg esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling.

Vedligeholdelsesbehandling med esketamin 28 mg*, 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og fra uge 9 hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen.

Komparator
Placebo, intranasalt, i kombination med SSRI eller SNRI, oralt.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har esketamin i kombination med SSRI eller SNRI sammenlignet med placebo i kombination med SSRI eller SNRI til voksne med moderat til svær behand-

* Patienter ≥ 65 år

lingsresistent depression vurderet ud fra MSM i den aktuelle moderate til svære depressive episode?

Population
Patienter over 18 år med moderat til svær behandlingsresistent depression bestemt som patienter, der ikke har responderet på to forskellige typer antidepressiva givet i tilstrækkelig dosis og tilstrækkelig lang tid (≥ 4 uger), eller har haft depression i to eller flere år (samme episode) uanset hvilken behandling og som har en score på 9 eller derover ud fra MSM.

Intervention
Induktionsfase med esketamin to gange ugentlig fra uge 0-4, startende med 28 mg* eller 56 mg esketamin plus nyligt initieret daglig oralt antidepressivum, som ikke har indgået i behandling tidligere, på dag 1 efterfulgt af administration med 28 mg, 56 mg eller 84 mg esketamin plus nyligt initieret daglig oralt antidepressivum ved efterfølgende behandling.

Vedligeholdelsesbehandling med esketamin 28 mg*, 56 mg eller 84 mg en gang ugentlig fra uge 5-8 og fra uge 9 hver anden uge eller ugentligt samt vedligeholdelse af oralt antidepressivum administreret under induktionsfasen.

Komparator
Placebo, intranasalt, i kombination med SSRI eller SNRI, oralt.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

* Patienter ≥ 65 år

Tabel 1 Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel der oplever alvorlige uønskede hændelser (SAE'er)	5 %-point
			Andel der ophører behandling	20 %-point
			Narrativ gennemgang af specifikke hændelser (se nærmere i tekst)	Ikke relevant
Remission	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score til hhv. ≤ 7 point og ≤ 11 point	15 %-point
Respons	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	HDRS-17 eller MADRS. Andel der reducerer score fra baseline med 50 %	20 %-point
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på WHO-5 eller EQ-5D i prioriteret rækkefølge	10 point/0,07 point

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

Generelt om måletidspunkter

To måletidspunkter, efter endt behandling (induktionsfasen) og efter endt opfølgning (endt vedligeholdelsesfase eller længst mulig follow-up), gælder for samtlige effektmål.

Måletidspunktet for endt behandling skal være minimum fire uger efter første administration ud fra rationalet om, at antidepressiva (komparator) først har begyndende effekt efter fire uger. Måletidspunktet for endt opfølgning skal være minimum seks måneder efter første administration ud fra rationalet om, at tilbagefald efter at have opnået remission af seks måneders varighed, ikke tæller som relaps, men tæller som en ny depressiv episode. De to måletidspunkter vægtes lige højt og anses af fagudvalget for at være et udtryk for hhv. en umiddelbar effekt af behandling og vedvarende (*sustained*) effekt af behandling. En umiddelbar effekt målt på remission eller respons kan muligvis have en akut antiselvmordseffekt, mens en vedvarende effekt anses for at være kurativ.

3.3.1 Kritiske effektmål

Uønskede hændelser

Alvorlige uønskede hændelser: Alvorlige uønskede hændelser (SAE'er) har stor betydning for den enkelte patients livskvalitet. Fagudvalget lægger vægt på, at der er tale om en behandling for en patientgruppe med en overhyppighed af selvmordsforsøg, der i samspil med de associative effekter af esketamin potentielt kan øge dødelighed og selvskade. Mindste klinisk relevante forskel vurderes af fagudvalget som en forskel på 5 %-point.

Fagudvalget ønsker behandlingsophør forårsaget af uønskede hændelser opgjort. Fagudvalget fremhæver, at der er tale om væsentligt syge patienter med tilsyneladende god mulighed for bedring. Derfor må der accepteres et vist niveau af behandlingsophør, hvis den andel af patienter, som forbliver i behandling, oplever en relevant bedring. Hvis der findes information om specifikke årsager til, at patienterne ophører behandling, vil fagudvalget også inddrage denne information i vurderingen af dette effektmål, idet frafald generelt er højt i studier indenfor depression, og i tilfælde, hvor der er tale om reversible, mindre alvorlige bivirkninger, vil være relevant at forsøge behandling på trods af risiko for behandlingsophør. Fagudvalget fastsætter den mindste klinisk relevante forskel til 20 %-point.

Fagudvalget vil foretage en kvalitativ gennemgang af uønskede hændelser og død uanset årsag. Der er en række specifikke hændelser som vil blive vurderet, dette indbefatter f.eks. udvalgte hændelser som f.eks. dissociative symptomer, mentale forstyrrelser, selvmordstanker og hypertension. Samtidig kan der være nogle særlige patientgrupper som fagudvalget vil være opmærksomme på i vurderingen af esketamin. Det kan f.eks. være patienter med høj alder i kombination med somatisk komorbiditet eller patienter med misbrug, psykiatrisk- eller anden somatisk komorbiditet. Gennemgangen vil tage udgangspunkt i publicerede studier, produktresuméer og EPAR med henblik på at vurdere, om der er forskel mellem grupperne mht. alvorlighed, håndterbarhed og hyppighed af uønskede hændelser og død uanset årsag.

Remission

Remission betyder, at patienten ikke længere har symptomer på depression. Depression og remission af depression måles ofte på sværhedsgraden af depressive symptomer på en skala som Hamilton Depression Rating Scale (HDRS) (interval 0-52 point) og Montgomery–Åsberg Depression Rating Scale (MADRS) (interval 0-60 point). HDRS er den mest almindeligt anvendte depressionsskala på verdensplan, herunder også i

Danmark. MADRS er udviklet med det formål at være mere følsom overfor de ændringer, der er forårsaget af antidepressiva, men der er en høj korrelation mellem de scorer, der opnås med hhv. HDRS og MADRS [19]. Fagudvalget vurderer, at remission kan opgøres med begge skalaer og anslår, at remissionsraten med den nuværende standardbehandling med antidepressiva hos patienter, som tidligere har svigtet på to behandlinger, er 13-14 %. Dette estimat er baseret på evidens fra STAR*D-studiet, som er en stor anerkendt undersøgelse, der bl.a. estimerer remisionsrater efter flere sekventielle behandlinger hos patienter med svær depression [20].

Den engelske HTA-institution NICE har tidligere foreslået en forskel på tre point på HDRS eller 0,5 standardiseret middelforskel (SMD) som klinisk betydende [21]. Disse grænsetærskler er siden blevet kritiseret og anbefales ikke længere, selvom de stadig anvendes som reference i flere kliniske forsøg [21]. Fagudvalget vurderer, at en forskel i andel, der reducerer scoren til, hvad der er beskrevet som et relativt nulpunkt, hhv. ≤ 7 på HDRS-17 og ≤ 11 på MADRS [22,23] uanset udgangspunkt og opgjort ved: 1) endt behandling, skal udgøre mindst 15 %-point og 2) efter længst mulig opfølgningstid, skal udgøre mindst 15 %-point for at være klinisk relevant.

3.3.2 Vigtige effektmål

Respons

Remission vurderes af fagudvalget at være svært opnåeligt hos patienter med behandlingsresistent depression. Når remission ikke kan opnås, har det stadig afgørende betydning for patienten, at den depressive tilstand bedres. Respons måles også, som det er tilfældet med remission vha. HDRS- eller MDRS-skalaen og betyder, at patienten som minimum har fået halveret sine symptomer målt som en reduktion i score på mindst 50 % fra baseline. Fagudvalget vurderer, at respons er et vigtigt effektmål til at vurdere en given effekt af behandlingen, da depressionssymptomer kan forværres eller bedres over ganske kort tid. Fagudvalget anslår, at responsraten med den nuværende standardbehandling med antidepressiva er 20 %. Fagudvalget vurderer, at en forskel i andel, der opnår respons opgjort ved: 1) endt behandling, skal udgøre mindst 20 %-point og 2) opgjort efter længst mulig opfølgningstid, skal udgøre mindst 20 %-point for at være klinisk relevant.

Livskvalitet

Fagudvalget er ikke bekendt med et værktøj til vurdering af livskvalitet, der er tilstrækkeligt valideret til patienter med behandlingsresistent depression. Fagudvalget mener, at en vurdering af livskvalitet ved hjælp af et generisk værktøj er behæftet med megen usikkerhed [24] og nedjusterer derfor livskvalitet fra et kritisk til et vigtigt effektmål. Fagudvalget ønsker livskvalitet opgjort med WHO-5. WHO-5 er et velvalideret generisk måleinstrument, der er udarbejdet for at kunne måle niveauet af mental sundhed ud fra trivsel og velbefindende. Spørgsmålene er formuleret positivt, men bliver også brugt til at vurdere negative aspekter af mental sundhed, eksempelvis ved screening af forøget risiko for depression [25]. Scoren går fra 0-100. Gennemsnittet for befolkningen som helhed er 68 pointtal, men ved pointtal over 50 er der ikke umiddelbart risiko for depression eller langvarig stressbelastning [26]. Pointtal mellem 0-35 angiver, at der er stor risiko for depression eller stressbelastning [26]. En forøgelse (eller forringelse) på 10

pointtal anses for en klinisk signifikant forskel, dvs. en forskel i trivsel, der er så stor, at den kan tilskrives indsatsen [26,27]. På denne baggrund fastsætter fagudvalget en mindste klinisk relevant forskel til 10 pointtal for WHO-5. Hvis der ikke findes data opgjort med WHO-5, ønsker fagudvalget livskvalitet opgjort med EQ-5D. EQ-5D er et velvalideret, generisk spørgeskema udfyldt af patienten til vurdering af livskvalitet [28]. Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression) og indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Fagudvalget er opmærksomt på, at 2 ud af 5 delskalaer i EQ-5D måler somatiske forhold (bevægelighed, smerter), som ikke nødvendigvis er relevante for mennesker med depression, og som i høj grad kan skyldes anden (somatisk) sygdom. Fagudvalget er ikke bekendt med en valideret mindste klinisk relevant forskel specifikt for depression og læner sig op ad amerikanske værdier og en mindste klinisk relevant forskel på mellem 0,05-0,08 i EQ-5D index score for posttraumatisk stresssyndrom [29]. Den mindste klinisk relevante forskel er på denne baggrund fastsat af fagudvalget til 0,07 point i EQ-5D index score.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den oprindelige foreløbige ansøgning blevet orienteret om, at der findes studier, hvor intranasal esketamin i kombination med antidepressiva er sammenlignet direkte med placebo i kombination med antidepressiva. Studierne er følgende:

Korttidsstudier

- TRANSFORM-1 (NCT02417064)
- TRANSFORM-2 (NCT02418585)
- TRANSFORM-3 (NCT02422186)

Vedligeholdelsesstudie

- SUSTAIN-1 (NCT02493868)

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

Medicinrådet er i en ny foreløbige ansøgning i december 2020 i forbindelse med genvurderingen, blevet orienteret om, at der findes yderligere, publicerede og upublicerede studier, der kan styrke datagrundlaget ift. overførbarheden af studieresultaterne til den danske population, sikkerheden af lægemidlet og især ift. at belyse langtidseffekterne af intranasal esketamin.

Studierne/data er følgende:

- SUSTAIN-2 (NCT01930188)
- SUSTAIN-3 (NCT01885208)
- SYNAPSE (NCT01998958)
- Upublicerede observationelle data fra rapport for *French National Agency for Medicines and Health Product Safety (ANSM)*
- Upublicerede observationelle data prospektivt kohortestudie *European Standard Clinical Practice*

Der er tilstrækkeligt datagrundlag til at besvare de kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal derudover konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.

- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).

- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundheds-økonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (*Grading of Recommendations, Assessments, Development and Evaluation*) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

På nuværende har ansøger ikke angivet en forventet behandlingsvarighed. Fagudvalget ønsker en vurdering af forventet varighed af behandling med esketamin.

Fagudvalget finder, at der er nogle praktiske aspekter, som må overvejes i forbindelse med Medicinrådets vurdering af esketamin som mulig standardbehandling. Esketamin skal administreres under kontrollerede forhold under opsyn af fagfolk indledningsvist to gange om ugen og under vedligeholdelsesfasen én gang om ugen eller hver anden uge. Dette anses af fagudvalget at være et stort indgreb i patienterne hverdag, særligt i det lys, at det endnu ikke vides, hvor længe patienterne forventes at være i behandling. Fagudvalget vurderer, at der potentielt kan opstå et adhærensproblem, som muligvis vil lede nogle patienter til selvmedicinering med ketamin i stedet eller lede dem til at afbryde behandlingen muligvis med alvorlige følger. Fagudvalget ønsker ansøgers refleksion over denne problemstilling.

Fagudvalget ønsker en opgørelse af, hvor mange events i form af mani, der er registreret under behandling og under follow-up. Baggrunden for dette er, at en andel af patienterne, der diagnosticeres med unipolar depression, har en underliggende bipolar lidelse.

Fagudvalget ønsker data på komorbiditet, f.eks. en oversigt over komorbiditeter, patienterne havde på inklusionstidspunktet til studierne. Baggrunden for dette er at bestemme heterogeniteten i studiepopulationen for at vurdere, om studiepopulationen er repræsentativ for patienter med behandlingsresistent depression, der ofte har andre psykiske eller somatiske lidelser.

Fagudvalget ønsker ændringer i MADRS-scoren præsenteret grafisk over perioden fra baseline til endt opfølgning som spaghetti-plots for de individuelle patienter med en score på 9 eller derover på MSM for at vurdere, om der er en sammenhæng mellem behandling og ændring i depressive symptomer over kortere tidsintervaller og/eller på individniveau.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning udarbejdet af Medicinrådet på området.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandlingsresistent depression

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Poul Videbech *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Ny udpegning igangsat	Region Nordjylland
Simon Hjerrild *Afdelingslæge*	Region Midtjylland
Claus Havregaard Sørensen *Overlæge*	Region Syddanmark
Dénes Langyel *Overlæge*	Region Sjælland
Lars Vedel Kessing *Professor, overlæge*	Region Hovedstaden
Sidsel Arnsbang Pedersen *Læge, ph.d.*	Dansk Selskab for Klinisk Farmakologi
Jonas Meile *Speciallæge i almen medicin*	Dansk Selskab for Almen Medicin
Klaus Martiny *Professor, overlæge*	Inviteret af formanden
Martin Balslev Jørgensen *Professor, overlæge*	Inviteret af formanden
Leni Grundtvig Nielsen *Patient/patientrepræsentant*	Danske Patienter
Louise Dahl Wulff *Patient/patientrepræsentant*	Danske Patienter

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	16. marts 2021	Godkendt af Medicinrådet