Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ofatumumab til behandling af attakvis multipel sklerose

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. ofatumumab, version 1.0
2. Forhandlingsnotat fra Amgros vedr. ofatumumab
3. Høringssvar fra ansøger vedr. lægemidlets værdi og den sundhedsøkonomiske afrapportering
4. Medicinrådets vurdering vedr. ofatumumab til behandling af attakvis multipel sklerose, version 1.0
5. Ansøgers endelige ansøgning
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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Ofatumumab

Attakvis multipel sklerose

Version 1.0

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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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspris
MS	Multipel sklerose
JCV	John Cunningham virus
s.c.	Subkutan
i.v.	Intravenøs
EDSS	*Expanded Disability Status Scale*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt for klinisk spørgsmål 1, er de inkrementelle omkostninger for ofatumumab ca. [redacted] DKK pr. patient sammenlignet med teriflunomid. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 110.000 DKK pr. patient. Hvis behandlingsvarigheden er på 3 år, hvilket er estimatet anvendt i Medicinrådets hovedanalyse, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK.

I det scenarie, Medicinrådet mener er mest sandsynligt for klinisk spørgsmål 2, er de inkrementelle omkostninger for ofatumumab ca. [redacted] DKK pr. patient sammenlignet med ocrelizumab. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. -64.000 DKK pr. patient. Med en behandlingsvarighed på 3 år, hvilket er estimatet anvendt i Medicinrådets hovedanalyse, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK.

De inkrementelle omkostninger er hovedsageligt drevet af forskelle i lægemiddelomkostninger. Disse er dog usikre og muligvis underestimerede. Det skyldes, at der er usikkerheder vedr. behandlingslængden, som potentielt har stor betydning for analysens resultat, da det netop er forskelle i lægemiddelomkostninger, der driver omkostningerne.

Analysen af budgetkonsekvenser er forbundet med betydelige usikkerheder, da en ny behandlingsvejledning er under udarbejdelse. Den kan medføre betydelige ændringer i valg af behandling og patientantal på første og anden linje. Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af ofatumumab som mulig standardbehandling i første linje (klinisk spørgsmål 1) vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 30,8 mio. DKK i det femte år. Ved anbefaling af ofatumumab som mulig standardbehandling i anden linje (klinisk spørgsmål 2) vurderer Medicinrådet, at budgetkonsekvenserne for regionerne vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -8,3 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af ofatumumab som mulig standardbehandling på danske hospitaler til første- og andenlinjebehandling af attakvis multipel sklerose.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Novartis. Medicinrådet modtog ansøgningen den 14. juni 2021.

3.1 Patientpopulation

Multipel sklerose (MS) er en kronisk inflammatorisk lidelse i centralnervesystemet, der typisk debuterer i alderen 20-40 år og forekommer ca. dobbelt så ofte hos kvinder som hos mænd. Ud over at være immunmedieret er sygdommens underliggende årsag ukendt. Der er dog fundet en række genetiske, miljømæssige og livstilsassocierede risikofaktorer [1,2].

Det er muligt at inddele MS i to overordnede kategorier: attakvis MS og progressiv MS. Attakvis MS er den hyppigste form for MS og er karakteriseret ved attakvise episoder med forværring af symptomer efterfulgt af perioder med bedring. MS kan yderligere kategoriseres i forhold til, om sygdommen er aktiv eller ikke-aktiv [3,4]. Med aktivitet menes der attakker eller forværring, som ses på scanninger. I Danmark lever omkring 17.000 personer med MS, og den årlige incidens er ca. 600 [5,6].

3.1.1 Subpopulationer

Lægemidler til behandling af attakvis MS er delt op i to grupper i Medicinrådets behandlingsvejledning og lægemiddelrekommandation [7,8], hhv. første og anden linje. Dette skal forstås således, at de mest effektive og potentielt mest bivirkningstunge lægemidler kaldes andenlinjelægemidler og forbeholdes patienter med størst sygdomsaktivitet eller patienter, hvor førstelinjebehandling viser sig ikke at være effektiv nok.

Patienterne, som behandles med førstelinjelægemidler, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret klinisk og radiologisk).

Patienter, som behandles med andenlinjelægemidler, er patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat og patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.2 Komparator

Medicinrådet har vurderet den kliniske værdi af ofatumumab på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har ofatumumab sammenlignet med teriflunomid for voksne patienter med aktiv attakvis MS og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

Klinisk spørgsmål 2:

Hvilken værdi har ofatumumab sammenlignet med ocrelizumab for voksne patienter med aktiv attakvis MS og høj sygdomsaktivitet (andenlinjebehandling)?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for ofatumumab sammenlignet med teriflunomid og ocrelizumab til hhv. første- og andenlinjebehandling. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved første- og andenlinjebehandling af attakvis multipel sklerose.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsmodel til at estimere omkostningerne forbundet med behandlingen med ofatumumab. Modellen inkluderer hændelser som administration af lægemidler, løbende monitorering samt attakker, men sygdomsprogression er ikke inkluderet i den sundhedsøkonomiske model.

Ansøger antager, baseret på resultaterne fra ASCLEPIOS I og ASCLEPIOS II [9], at der til klinisk spørgsmål 1 er en klinisk meningsfuld forskel i effekt på sandsynligheden for attakker mellem ofatumumab og teriflunomid. I modellen anvendes den årlige attakrate fra ovennævnte studier til at estimere omkostningerne forbundet med håndtering af attaker, når patienterne behandles med hhv. ofatumumab eller teriflunomid. For klinisk spørgsmål 2 antager ansøger, at der, baseret på en narrativ sammenligning, ikke er forskel i effekt på sandsynligheden for attakker mellem ofatumumab og ocrelizumab. Den narrative sammenligning er lavet ud fra studierne OPERA I og OPERA II [10], som sammenligner ocrelizumab med interferon beta-1a.

Ansøger antager, at den gennemsnitlige behandlingslængde med ofatumumab, teriflunomid og ocrelizumab er 3 år. Dette estimat er baseret på Medicinrådets tidligere vurdering af ozanimod til behandling af attakvis MS, hvor der ligeledes indgik et klinisk spørgsmål for både første- og andenlinjebehandling. Her blev det af fagudvalget vurderet, at den gennemsnitlige behandlingstid for både første- og andenlinjelægemidlerne var 3 år.

Medicinrådets vurdering af ansøgers model
Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 3 år.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet pointerer, at behandlingen med præparaterne i denne analyse ikke er tidsbegrænset. Det vil sige, at stabile patienter uden nævneværdige bivirkninger kan behandles med ofatumumab, teriflunomid og ocrelizumab i flere år, herunder også over 3 år, men Medicinrådet accepterer ansøgers tilgang, da Medicinrådet vurderer, at den gennemsnitlige behandlingstid ca. er 3 år for de tre præparater. Det understreges, at der er usikkerheder forbundet med dette estimat. Medicinrådet er opmærksom på, at lægemidlerne i den nuværende behandlingsvejledning for attakvis multipel sklerose er sammenlignet på baggrund af en tidshorisont på hhv. 1 år for førstelinjebehandling og 4 år for andenlinjebehandling. Sekretariatet udfører følsomhedsanalyser, hvor behandlingslængden varieres for at belyse usikkerheden forbundet med behandlingslængden af ofatumumab, teriflunomid og ocrelizumab.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af ofatumumab sammenlignet med teriflunomid og ocrelizumab. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, omkostninger ved attakker og patientomkostninger. Ansøger har ekskluderet omkostninger til bivirkninger, da ansøger argumenterer for, at der ikke er demonstreret signifikante forskelle i den generelle kliniske sikkerhed.

4.2.1 Lægemiddelomkostninger

Ansøger anvender de lægemiddeldoseringer, som er angivet i produktresuméerne for ofatumumab, teriflunomid og ocrelizumab:

- Ofatumumab: 20 mg subkutant (s.c.) hver fjerde uge
- Teriflunomid: 14 mg oralt én gang dagligt

- Ocrelizumab: 600 mg intravenøst (i.v.) én gang hver sjette måned.

Behandling med ofatumumab indledes af 20 mg s.c. doseringer i uge 0, 1 og 2 af behandlingen. For behandling med ocrelizumab deles første dosis af 600 mg i to intravenøse doseringer, således at 300 mg administreres intravenøst i uge 0 og uge 2. Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP (november 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Ofatumumab	20 mg	1 stk.	[redacted]	Amgros
Teriflunomid	14 mg	28 stk.	[redacted]	Amgros
	14 mg	84 stk.	[redacted]	
Ocrelizumab	300 mg	1 stk.	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger antager, at ofatumumab administreres s.c. i hjemmet af patienten selv, og at der derfor kun inkluderes administrationsomkostninger ved første administration. For ocrelizumab har ansøger inkluderet administrationsomkostninger for alle administrationer, da disse foregår i.v. på hospitalet. Der inkluderes ikke administrationsomkostninger for teriflunomid, da det gives peroralt i hjemmet. Administrationsomkostninger for både ofatumumab og ocrelizumab er af ansøger takseret med en 2021 DRG-takst.

Ansøger har valgt at ekskludere omkostninger til præmedicinering for behandling med ocrelizumab, da ansøger vurderer, at omkostningerne vil være minimale og derfor ikke vil være udslagsgivende for det samlede resultat. Ligeledes argumenterer ansøger for, at det er en konservativ tilgang, da det favoriserer ocrelizumab.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet vurderer, at der kan være få patienter, som har brug for overvågning i forbindelse med administration af ofatumumab – ud over ved den første administration – eventuelt ved en hjemmesygeplejerske. Medicinrådet vurderer dog kun, at dette vil være et fåtal og svært at kvantificere. Medicinrådet accepterer derfor ansøgers tilgang. Anvendte enhedsomkostninger kan ses i Tabel 2.

Tabel 2. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kode	Kilde
Administrationsomkostninger (både s.c. og i.v.)	3.353,00	01MA98	[DRG-2021]

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger har inkluderet omkostninger til monitorering af patienter, herunder løbende MR-scanninger, klinisk kontrol afhængigt afEDSS-score og omkostninger for løbende blodprøvekontroller. Alle monitoreringsomkostninger takseres med 2021 DRG-takster. Ansøger antager, at monitoreringsomkostninger for ofatumumab og ocrelizumab er identiske, da virkningsmekanismen for de to lægemidler er den samme.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af monitoreringsomkostninger. Anvendte omkostninger for MR-scanning, klinisk kontrol med EDSS-score og blodprøvekontroller er vist i Tabel 3, mens frekvenserne er præsenteret i Tabel 4.

Tabel 3. Omkostninger til monitorering

	Enhedsomkostning [DKK]	Kode	Kilde
MR-scanning	2.319,00	30PR03	[DRG-2021]
Klinisk kontrol med EDSS-score	3.353,00	01MA98	[DRG-2021]
Blodprøvekontrol	129,00	65TE01	[DRG-2021]

Tabel 4. Frekvens af alle monitoreringsomkostninger

	Ofatumumab			Teriflunomid			Ocrelizumab		
	År 1	År 2	År 3+	År 1	År 2	År 3+	År 1	År 2	År 3+
MR-scanning	2	1	1	2	1	1	2	1	1
Klinisk kontrol med EDSS-score	3	2	2	2	2	1	3	2	2
Blodprøvekontrol	3	2	2	7	2	2	3	2	2

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Omkostninger til håndtering af attakker

Ansøger har inkluderet omkostninger forbundet med attakker, da ansøger antager, at ofatumumab har en klinisk meningsfuld effekt på sandsynligheden for attakker sammenlignet med teriflunomid i førstelinjebehandling. Dette baseres på data fra ASCLEPIOS I og ASCLEPIOS II, hvor ansøger argumenterer for en bedre årlig attakrate for ofatumumab. I ASCLEPIOS I rapporteres en årlig attakrate på 0,11 og 0,10 og i ASCLEPIOS II en årlig attakrate på 0,22 og 0,25 for hhv. ofatumumab og teriflunomid. Ud fra disse har ansøger estimeret en samlet årlig attakrate baseret på antallet af patienter i de to studier, så den samlede årlige attakrate for ofatumumab er 0,10, hvor den for teriflunomid er 0,24, se Tabel 5.

Tabel 5. Årlig attakrate for ofatumumab og teriflunomid

	Årlig attakrate i ASCLEPIOS I	Årlig attakrate i ASCLEPIOS II	Samlet årlig attakrate
Ofatumumab	0,11	0,22	0,10
Teriflunomid	0,10	0,25	0,24

Ansøger inkluderer attakomkostninger som omkostninger pr. attak. Ansøger anvender attakomkostninger fra det danske *cost of illness-studie, Vestergaard et al.* [11], hvor omkostningen pr. attak er estimeret som forskellen i omkostninger til ressourceforbrug mellem patienter med en EDSS-score på 0-6, der oplever attakker og ikke oplever attakker over en tremåneders periode. Fremskrevet til 2021-værdier antager ansøger, at omkostninger pr. attak er 19.891 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger til håndtering af attakker

Medicinrådet accepterer ikke ansøgers tilgang til estimering af omkostninger til håndtering af attakker, da ansøger ikke har redegjort for, hvad disse attakomkostninger indeholder. Medicinrådet inddrager derfor ikke attaktomkostninger i hovedanalysen. Medicinrådet vurderer dog, at der vil være omkostninger til håndtering af attakker, men at disse vil variere mellem patienter og er svære at kvantificere. Medicinrådet vælger derfor at udføre en følsomhedsanalyse, hvor ansøgers attakomkostninger anvendes.

Medicinrådet accepterer ikke ansøgers tilgang vedr. attakomkostninger, men vælger at udføre en følsomhedsanalyse, hvor disse inkluderes.

Bivirkningsomkostninger

Ansøger har ikke inkluderet omkostninger til håndtering af bivirkninger, da ansøger argumenterer for, at der ikke er demonstreret signifikante forskelle i den generelle kliniske sikkerhed mellem ofatumumab, teriflunomid og ocrelizumab.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers tilgang, da data for nuværende ikke indikerer en forskel i bivirkningsfrekvenser. Fagudvalget udtrykker dog en bekymring for, at

ocrelizumab og ofatumumab på længere sigt kan give risiko for flere alvorlige bivirkninger (f.eks. genstridige infektioner). Dette er dog meget usikkert.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid, transporttid og tid brugt på selvadministration af ofatumumab i hjemmet. Ansøger antager, at det tager 10 minutter pr. administration af ofatumumab i hjemmet. Derudover har ansøger antaget, at tidsforbruget for administration af ocrelizumab på hospitalet er 150 minutter for selve infusionen og 60 minutter til efterfølgende overvågning.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,52 DKK/km med en gennemsnitlig afstand på 28 km pr. besøg (14 km frem og tilbage), jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, som kan ses i Tabel 6.

Tabel 6. Estimat af effektiv patienttid

	Patienttid [minutter]
Selvadministration af ofatumumab i hjemmet	10
Infusion af ocrelizumab	150
Overvågning efter infusion af ocrelizumab	60

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

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 en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Ansøger har udarbejdet separate følsomhedsanalyser for klinisk spørgsmål 1.

Følsomhedsanalyser udført til klinisk spørgsmål 1 er præsenteret i Tabel 7.

Tabel 7. Følsomhedsanalyser for klinisk spørgsmål 1 og beskrivelse

Følsomhedsanalyse	Beskrivelse
Omkostninger til attakker	+/- 20 %
Tidshorisont sænkes	12 måneders tidshorisont
Tidshorisont øges	60 måneders tidshorisont
Lægemiddelspild	Én måneds lægemiddelspild for ofatumumab inkluderet

Følsomhedsanalyser udført til klinisk spørgsmål 2 er præsenteret i Tabel 8.

Tabel 8. Følsomhedsanalyser for klinisk spørgsmål 2 og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont sænkes	12 måneders tidshorisont
Tidshorisont øges	60 måneders tidshorisont
Lægemiddelspild	Én måneds lægemiddelspild for ofatumumab inkluderet

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vurderer, at ansøgers følsomhedsanalyser bidrager med information om analysens usikkerhed, og Medicinrådet vælger derfor at præsentere dem. I Medicinrådets hovedanalyse ekskluderes attakomkostninger, og derfor erstattes ansøgers følsomhedsanalyse af attakomkostningerne med en følsomhedsanalyse, hvor attakomkostninger inkluderes.

Medicinrådet vælger at præsentere ansøgers følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne i hhv. ansøgers og Medicinrådets hovedanalyse.

Tabel 9. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	3 år	3 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Attakomkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Attakomkostninger Patientomkostninger
Dosering		
Ofatumumab	20 mg én gang hver 4. uge	20 mg én gang hver 4. uge
Teriflunomid	14 mg én gang dagligt	14 mg én gang dagligt
Ocrelizumab	600 mg én gang hver 6. måned	600 mg én gang hver 6. måned
Behandlingslængder	3 år for både ofatumumab, teriflunomid og ocrelizumab	3 år for både ofatumumab, teriflunomid og ocrelizumab
Inkludering af spild	Kun for ofatumumab i sensitivitetsanalyse for klinisk spørgsmål 2	Kun for ofatumumab i sensitivitetsanalyse for klinisk spørgsmål 2
Omkostninger ved attakker	Inkluderet	Ekskluderet

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse for de to kliniske spørgsmål bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 9.

For klinisk spørgsmål 1 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 110.000 DKK. Med en behandlingsvarighed på 3 år, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK.

Resultaterne fra Medicinrådets hovedanalyse for klinisk spørgsmål 1 er præsenteret i Tabel 10.

Tabel 10. Resultatet af Medicinrådets hovedanalyse ved sammenligning med teriflunomid, DKK, diskonterede tal

	Ofatumumab	Teriflunomid	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	36.072	26.752	9.320
Attakomkostninger	0	0	0
Patientomkostninger	4.595	4.070	524
Totale omkostninger	[redacted]	[redacted]	[redacted]

For klinisk spørgsmål 2 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK i Medicinrådets hovedanalyse. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient -64.000 DKK. Med en behandlingsvarighed på 3 år, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK.

Resultaterne fra Medicinrådets hovedanalyse for klinisk spørgsmål 2 er præsenteret i Tabel 11.

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ocrelizumab, DKK, diskonterede tal

	Ofatumumab	Ocrelizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	36.072	55.517	- 19.445

	Ofatumumab	Ocrelizumab	Inkrementelle omkostninger
Attakomkostninger	0	0	0
Patientomkostninger	4.595	8.328	- 3.734
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 12.

Tabel 12. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger	
	Klinisk spørgsmål 1 [teriflunomid]	Klinisk spørgsmål 2 [ocrelizumab]
Resultatet af hovedanalysen	[redacted]	[redacted]
Inkludering af attakomkostninger	[redacted]	[redacted]
Tidshorisont på 5 år	[redacted]	[redacted]
Tidshorisont på 1 år	[redacted]	[redacted]
Én måneds lægemiddelspild for ofatumumab inkluderet	[redacted]	[redacted]

6. Budgetkonsekvenser

Analysen af budgetkonsekvenserne pr. år er forbundet med betydelige usikkerheder, da en ny behandlingsvejledning er under udarbejdelse. Den kan medføre betydelige ændringer i valg af behandling og patientantal på første og anden linje.

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

- Ofatumumab bliver anbefalet som mulig standardbehandling af Medicinrådet til både første- og andenlinjebehandling.
- Ofatumumab bliver ikke anbefalet som mulig standardbehandling.
- Ofatumumab bliver ikke anbefalet som mulig standardbehandling til førstelinjebehandling, men bliver anbefalet som mulig standardbehandling af Medicinrådet til andenlinjebehandling.

6.1 Estimat af patientantal og markedsandel

Ansøger har baseret sine antagelser vedr. patientantallet, der kandiderer til behandling med ofatumumab, på data fra Sclerosebehandlingsregistret. Ansøger vurderer, at ofatumumab vil overtage markedsandele fra hhv. dimethylfumurat i 1. linje og fingolimod i 2. linje, såfremt lægemidlet anbefales.

Ansøger anvender omkostningerne for hhv. dimethylfumurat og fingolimod direkte fra Medicinrådets omkostningsanalyse af ligestillede lægemidler til behandling af attakvis multipel sklerose, mens lægemiddelpriserne fremgår af bilag. Ansøger har ikke inkluderet natalizumab som en potentiel komparator for de JCV-negative patienter, selvom ca. 80 % af disse patienter bliver behandlet med natalizumab jf. behandlingsvejledningen.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Sekretariatet gør opmærksom på, at der er mange usikkerheder forbundet med ansøgers antagelser. Estimater af markedsandele er i denne vurdering problematiske, da der er en ny behandlingsvejledning under udarbejdelse, og markedsandelene vil i høj grad afhænge af rækkefølgen i den efterfølgende lægemiddelrekommandation. I behandlingsvejledningen vil fagudvalget bl.a. forsøge at definere kriterier for høj sygdomsaktivet, hvilket kan ændre på fordelingen af patienter mellem første og anden linje. Derfor er det svært at basere et estimat af patientantal på den nuværende rekommandation, og budgetkonsekvensanalysen må betragtes som yderst usikker.

Fagudvalget er blevet konsulteret i forhold til patientantal, hvis ofatumumab anbefales som mulig standardbehandling, og hvis ikke ofatumumab anbefales. Fagudvalget estimerer, at ca. 300 patienter pr. år forventes at være kandidater til førstelinjebehandling, se Tabel 13. Fagudvalget vurderer, at ofatumumab ikke er relevant til patienter i førstelinjebehandling. Medicinrådet har alligevel udregnet budgetkonsekvenserne ved en anbefaling på første linje. I det scenarie antager

Medicinrådet, at ofatumumab vil overtage størstedelen af nye patienter, hvis ofatumumab bliver anbefalet. Hvis ofatumumab ikke bliver anbefalet, vil markedet forblive som den nuværende lægemiddelrekommandation. Derfor antager Medicinrådet for simplicitet, at ofatumumab, hvis anbefalet, vil opnå et markedsoptag på 95 %, mens de resterende 5 % går til det nuværende 1. valg (teriflunomid). Medicinrådet fremhæver dog, at dette er en meget simplificeret tilgang. Medicinrådet antager, at hvis ofatumumab ikke bliver anbefalet, vil det nuværende 1. valg i lægemiddelrekommandationen (teriflunomid) beholde 95 % af markedet, og de resterende 5 % vil gå til det nuværende 2. valg (dimethylfumarat) og dermed 0 % til ofatumumab.

Tabel 13. Medicinrådets estimat af antal patienter pr. år for førstelinjebehandling

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ofatumumab	285	285	285	285	285
Teriflunomid	15	15	15	15	15
Dimethylfumarat	0	0	0	0	0
			Anbefales ikke		
Ofatumumab	0	0	0	0	0
Teriflunomid	285	285	285	285	285
Dimethylfumarat	15	15	15	15	15

Fagudvalget estimerer, at ca. 200 patienter pr. år forventes at være kandidater til behandling med ofatumumab til andenlinjebehandling, se Tabel 14. Fagudvalget vurderer ligeledes, at andenlinjebehandling vil ske i henhold til den gældende behandlingsvejledning og tilhørende lægemiddelrekommandation. Derfor antager Medicinrådet, at ofatumumab vil blive anvendt til behandling af 80 % af alle nye patienter som er JCV positive, hvis ofatumumab både bliver anbefalet og samtidig bliver førstevalget i lægemiddelrekommandationen, mens de resterende 20 % af patienterne vil blive behandlet med det nuværende 1. valg (ocrelizumab). Hvis ofatumumab ikke bliver anbefalet, antager Medicinrådet, at 80 % af markedet vil forblive ved det nuværende 1. valg, mens de resterende 20 % af patienterne vil modtage behandling med det nuværende 2. valg (fingolimod). Fagudvalget vurderer, at man ikke som konsekvens af en eventuel anbefaling af ofatumumab vil skifte behandling blandt patienter, der allerede er i behandling med andre lægemidler, hverken i første eller anden linje. Medicinrådet understreger desuden, at det bidrager med usikkerhed, at ansøger ikke har inkluderet natalizumab som en mulig komparator for de JCV-negative patienter.

Tabel 14. Medicinrådets estimat af antal patienter pr. år for andenlinjebehandling

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ofatumumab	160	160	160	160	160
Ocrelizumab	40	40	40	40	40
Fingolimod	0	0	0	0	0
			Anbefales ikke		
Ofatumumab	0	0	0	0	0
Ocrelizumab	160	160	160	160	160
Fingolimod	40	40	40	40	40

Medicinrådet accepterer ikke ansøgers tilgang vedr. patientantallet i budgetkonsekvensanalysen og vælger at justere det i henhold til fagudvalgets vurdering samt nuværende lægemiddelrekommandation. Medicinrådet fremhæver desuden, at det bidrager med usikkerhed, at ansøger ikke har inkluderet natalizumab som en mulig komparator for de JCV-negative patienter.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Patientantallet og markedsoptaget justeres, jf. afsnit 6.1.

Medicinrådet estimerer, at anvendelse af ofatumumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling for klinisk spørgsmål 1. Resultatet er præsenteret i Tabel 15.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 30,8 mio. DKK i år 5.

Tabel 15. Medicinrådets analyse af totale budgetkonsekvenser for 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]

Medicinrådet estimerer, at anvendelse af ofatumumab vil resultere i

budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling for klinisk spørgsmål 2. Resultatet er præsenteret i Tabel 16.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. -8,3 mio. DKK i år 5.

Tabel 16. Medicinrådets analyse af totale budgetkonsekvenser for 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]

7. Diskussion

Behandling med ofatumumab er forbundet med inkrementelle omkostninger på [redacted] og [redacted] DKK sammenlignet med hhv. teriflunomid (klinisk spørgsmål 1) og ocrelizumab (klinisk spørgsmål 2). De inkrementelle omkostninger er næsten udelukkende drevet af forskelle i lægemiddelomkostninger.

Den sundhedsøkonomiske analyse er behæftet med usikkerhed på flere parametre. De væsentligste usikkerheder vedrører behandlingslængden og omkostninger til håndtering af attakker og bivirkninger.

I analysen er anvendt en tidshorisont på 3 år for både første- og andenlinjebehandling. Medicinrådet pointerer, at behandlingen med præparaterne i denne analyse ikke er tidsbegrænset. Det vil sige, at stabile patienter uden nævneværdige bivirkninger kan behandles med ofatumumab, teriflunomid og ocrelizumab i flere år, herunder også over 3 år, men Medicinrådet vurderer, at den gennemsnitlige behandlingstid ca. er 3 år for de tre præparater. Dette er dog usikkert, og følsomhedsanalyserne viser, at de inkrementelle omkostninger [redacted] med ca. [redacted] DKK for klinisk spørgsmål 1 og [redacted] med yderligere [redacted] DKK for klinisk spørgsmål 2, hvis tidshorisonten øges til 5 år. Tilsvarende [redacted] de inkrementelle omkostninger med [redacted] DKK for klinisk spørgsmål 1 og [redacted] med [redacted] DKK for klinisk spørgsmål 2, hvis tidshorisonten reduceres til 1 år.

Slutteligt vurderer Medicinrådet, at der er usikkerhed vedr. bivirkningsomkostningerne for ocrelizumab og ofatumumab, da fagudvalget udtrykker bekymring for, at disse lægemidler på længere sigt kan give risiko for flere alvorlige bivirkninger (f.eks. genstridige infektioner). Dette er dog meget usikkert. Effekten på de inkrementelle omkostninger er svære at kvantificere, [redacted]

Ansøger har baseret omkostninger til håndtering af attakker på et dansk *cost of illness-studie,* Vestergaard et al. [11], men hverken ansøger eller Vestergaard et al. [11], har redegjort for, hvad disse indeholder, og hvilke frekvenser og enhedsomkostninger der er anvendt. Medicinrådet vælger derfor at ekskludere disse omkostninger, men vurderer, at omkostninger til håndtering af attakker forventeligt vil være lavere for ofatumumab end teriflunomid for patienter i førstelinjebehandling. Det skyldes, at antallet af attaker er lavere ved behandling med ofatumumab end teriflunimod. En følsomhedsanalyse viser, at de inkrementelle omkostninger [redacted] med ca. [redacted] DKK, hvis ansøgers antagelser vedr. håndtering af attakomkostninger anvendes.

8. Referencer

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7. Medicinrådet. Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til attakvis multiepl sklerose. 2019.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. januar 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] og [redacted] DKK sammenlignet med hhv. teriflunomid (klinisk spørgsmål 1) og ocrelizumab (klinisk spørgsmål 2). Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 101.000 og -64.000 DKK for hhv. teriflunomid (klinisk spørgsmål 1) og ocrelizumab (klinisk spørgsmål 2). De fulde resultater er præsenteret i Tabel 17 og Tabel 18.

Tabel 17. Resultatet af ansøgers hovedanalyse, klinisk spørgsmål 1, DKK, diskonterede tal

	Ofatumumab	Teriflunomid	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	36.072	26.752	9.320
Attakomkostninger	6.385	15.433	- 9.048
Patientomkostninger	4.595	4.070	524
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 18. Resultatet af ansøgers hovedanalyse, klinisk spørgsmål 2, DKK, diskonterede tal

	Ofatumumab	Ocrelizumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	36.072	55.517	-19.445
Attakomkostninger	6.385	6.385	0
Patientomkostninger	4.595	8.328	-3.734
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Lægemiddelomkostninger for ekstra lægemidler i budgetkonsekvensanalysen

Ansøger anvender de lægemiddeldoseringer, som er angivet i produktresuméerne for dimethylfumarat og fingolimod:

- Dimethylfumarat: 240 mg oralt to gange dagligt (startdosis de første 7 dage er 120 mg oralt to gange dagligt)
- Fingolimod: 0,5 mg oralt én gang dagligt.

Medicinrådet har udskiftet AIP med SAIP for lægemidlerne, se Tabel 19.

Tabel 19. Anvendte lægemiddelpriser, SAIP (november 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Dimethylfumarat	240 mg	56 stk.	[redacted]	Amgros
	120 mg	14 stk.	[redacted]	
Fingolimod	1 mg	7 stk.	[redacted]	Amgros

10.3 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 ofatumumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK for klinisk spørgsmål 1, mens det for klinisk spørgsmål 2 vil resultere i et fald på [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 20.

Tabel 20. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
			Klinisk spørgsmål 1 (teriflunomid)		
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Klinisk spørgsmål 2 (ocrelizumab)		
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26. januar 2022
Leverandør	Novartis
Lægemiddel	Ofatumumab (Kesimpta)
Ansøgt indikation	Attakvis multipel sklerose

Forhandlingsresultat

Amgros har opnået følgende pris på Ofatumumab:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Aktuel SAIP (DKK)	Rabatprocent ift. AIP
Ofatumumab	20 mg/s.c.	1 stk. pen	10.800	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 2: Sammenligning af lægemiddelpriser. Baseret på behandlingsvejledningen

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Dosering	Pakningspris SAIP* (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
1. linje behandling						
Teriflunomid (Aubagio)	14 mg / PO	84 stk (blister)	14 mg 1x dagligt	[redacted]	5096 mg (52 uger)	[redacted]
Dimethylfumarat (Tecfidera)	240 mg / PO	56 stk (blister)	240 mg 2x dagligt	[redacted]	174.720 mg (52 uger)	[redacted]
2. linje behandling						
Ocrelizumab (Ocrevus)	300 mg / IV	1 stk	300 mg uge 0 og 2 + 600 mg hver 6 md.	[redacted]	1200 mg (48 uger)	[redacted]
Ofatumumab (Kesimpta)	20 mg/ SC	1 stk	20 mg hver 4. uge	[redacted]	240 mg (48 uger)	[redacted]
Ozanimod (Zeposia) (Nyt lægemiddel)	0,92 mg / PO	28 stk	0,92 mg 1x dagligt	[redacted]	309 mg (48 uger)	[redacted]

*priser pr. jan 2022

Status fra andre lande

Norge: Endnu ikke under vurdering.

Sverige: Godkendt til begrænset brug. Oktober 2021.[1]

England: Godkendt.[2] Maj 2021.

[1] https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2021-10-22-kesimpta-ingar-i-hogkostnadsskyddet-med-begransning.html

[2] https://www.nice.org.uk/guidance/TA699/chapter/1-Recommendations

Konklusion

[redacted]

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Til Medicinrådet

14. december 2021

Høringssvar til vurderingsrapporten for ofatumumab til behandling af attakvis multipel sklerose (RMS)

Kære Medicinråd,

Vi har den 30. november modtaget Medicinrådets endelige vurdering af klinisk merværdi for ofatumumab til behandling af RMS.

Novartis tager den markant ændrede kategorisering af merværdi af ofatumumab vs. teriflunomid i første linje i den endelige vurderingsrapport ift. kategoriseringen i udkastet til vurderingsrapporten ad notam.

Vi har følgende kommentarer til ændringen, som indebærer, at "moderat merværdi" i første linje ændres til "kan ikke kategoriseres", selvom ofatumumab metodemæssigt burde kunne tildeles merværdi:

Fagudvalget anerkender tydeligt den kliniske værdi af ofatumumab, idet de "bemærker, at en signifikant forskel på 4,9 %-point i, hvor stor en andel patienter, der oplever en vedvarende sygdomsforværring efter 2 års opfølgningstid, er et markant resultat inden for behandling af attakvis MS. Fagudvalget argumenterer yderligere med, at de antager, at ofatumumabs effekt på at bremse den vedvarende sygdomsforværring akkumuleres henover behandlingsperioden, og at effekten derfor vil have en markant klinisk relevans for patienter med attakvis MS".

Medicinrådet vurderer, at "patienterne i det kliniske studie er fulgt i for kort tid til at dokumentere, om ofatumumab kan forsinke, at sygdommen udvikler sig på længere sigt vs. teriflunomid". I ASCLEPIOS studierne har Novartis anvendt et innovativt statistisk design, hvor studiet er blevet afsluttet baseret på antallet af blindede hændelser. Dette design sikrede, at patienterne ikke forblev på en lav-effektiv behandling længere end nødvendigt og havde mulighed for tidligere at skifte til det open-label 5 års opfølgningsstudie ALITHIOS. Den mediane behandlingstid i ASCLEPIOS studierne var 1,6 år (svarende til 19 måneder). Til sammenligning var behandlingstiden i registreringsstudierne 24 og 19 måneder for teriflunomid og 22 måneder (svarende til 96 uger eller 1,8 år) for ocrelizumab.

For klinisk spørgsmål 1 anfører Medicinrådet, at "det er pga. usikkerhed omkring balancen mellem effekt og risiko for langsigtede alvorlige bivirkninger for gruppen af patienter med gennemsnitlig sygdomsaktivitet, at Medicinrådet ikke kan kategorisere lægemidlets værdi". Novartis bemærker, at det er yderst sjældent, at et nyt lægemiddel har langtidsdata på markedsføringstidspunktet.

De langtidsbivirkninger, som Fagudvalget fremhæver, er late-onset neutropeni, opportunistiske infektioner (herunder progressive multifocal leukoencephalopathy (PML)), reduceret vaccinerespons, faldende IgG niveauer samt malignitet. Novartis følger løbende disse hændelser i opfølgningsstudiet ALITHIOS. Der pågår vaccinestudier, bla. med Covid-19

vaccinerne, og vi vil i den udstrækning, det er muligt, dele de tilgængelige data med Medicinrådet i forbindelse med den igangværende opdatering af behandlingsvejledningen for multipel sklerose, forventeligt i starten af januar 2022. Novartis bemærker, at i henhold til de gældende Risk Management Planer er PML og nedsat leukocyt og lymfocyttal kendte vigtige risici for førstelinjebehandlingen dimethylfumarat, at PML er en potentiel vigtig risiko for teriflunomid, ocrelizumab og ofatumumab, samt at malignitet er en potentiel vigtig risiko for alle fire nævnte lægemidler.

Med hensyn til brug ved ønske om graviditet og under graviditet gør Novartis, som i ansøgningen, opmærksom på, at repleteringstiden er markant kortere for ofatumumab end for ocrelizumab (24,6 vs 72,0 uger). For både ofatumumab og ocrelizumab gælder, at de bør undgås under graviditeten. I modsætning til teriflunomid kan begge lægemidler imidlertid anvendes, såfremt den potentielle fordel for moderen opvejer den potentielle risiko for fosteret. Med hensyn til amning kan kvinder, som er behandlet med ofatumumab i de sidste måneder af graviditeten, amme umiddelbart efter fødslen, og andre kan starte behandling få dage efter fødslen, når der ikke mere udskilles IgG antistoffer i mælken. Brug af ocrelizumab og dimethylfumarat frarådes under amning, og teriflunomid er kontraindiceret.

Vi gør afslutningsvis opmærksom på, at Novartis i høringssvaret til den foreløbige vurderingsrapport dateret 19. november 2021 har argumenteret imod, at evidensens kvalitet for klinisk spørgsmål 1 er vurderet som "meget lav".

Vi ser frem til Medicinrådets endelige beslutning om ibrugtagning af ofatumumab i januar 2022.

Med venlig hilsen,
Novartis Healthcare A/S

Alice Brinch Mørch
Value and Access Manager, MD

Links til Summary RMP, fra EMAs hjemmeside:
Tecfidera (dimethylfumarat)
Aubagio (teriflunomid)
Ocrevus (ocrelizumab)
Kesimpta (ofatumumab)

Medicinrådet

Medicinrådets vurdering vedrørende ofatumumab til behandling af attakvis multipel sklerose

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	29. november 2021
Dokumentnummer	128214
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Klinisk spørgsmål 1

Medicinrådet vurderer, at patienterne i det kliniske studie er fulgt i for kort tid til at dokumentere om ofatumumab kan forsinke, at sygdommen udvikler sig på længere sigt. Data indikerer dog, at ofatumumab kan være et mere effektivt lægemiddel end teriflunomid. Ofatumumab har en moderat merværdi på de relative effektforskelle for vedvarende sygdomsforværring og attakrate, men de absolutte effektforskelle overstiger ikke de mindste klinisk relevante forskelle. Derfor konkluderer Medicinrådet, at værdien af ofatumumab til patienter med gennemsnitlig sygdomsaktivitet ikke kan kategoriseres efter Medicinrådets metoder sammenlignet med teriflunomid

Det er pga. usikkerhed omkring balancen mellem effekt og risiko for langsigtede alvorlige bivirkninger for gruppen af patienter med gennemsnitlig sygdomsaktivitet, at Medicinrådet ikke kan kategorisere lægemidlets værdi.

Klinisk spørgsmål 2

Medicinrådet konkluderer, at værdien af ofatumumab til patienter med høj sygdomsaktivitet ikke kan kategoriseres efter Medicinrådets metoder sammenlignet med ocrelizumab. Medicinrådet vurderer ud fra de tilgængelige data, at ofatumumab hverken har dårligere effekt eller sikkerhedsprofil end ocrelizumab. Medicinrådet bemærker, at der er større usikkerhed ved ofatumumab end ocrelizumab angående risiko for langsigtede bivirkninger.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 30. november 2021

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 standardbehandling. 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 (f.eks. 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

AR	*Adverse Reaction*
CDP	*Confirmed Disabilty Progression*
CDW	*Confirmed Disability Worsening*
CI:	Konfidensinterval
CrI	*Credible Interval*
DMT	*Disease Modifying Therapy*
EDSS	*Expanded Disability Status Scale*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
JCV	John Cunningham virus
MR	Magnetisk Resonans
MS	Multipel sklerose
MSQOL-54	*Multiple Sclerosis Quality of Life-54*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PML	Progressiv multifokal leukoencefalopati
PP:	*Per Protocol*
PPMS	Primær progressiv multipel sklerose
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RMS	Relapserende multipel sklerose
RR:	Relativ risiko
RRMS	Recidiverende relapserende multipel sklerose
SDMT	*Symbol Digit Modality Test*
SMD	*Standardized Mean Difference*
SPMS	Sekundær progressiv multipel sklerose

3. Introduktion

Formålet med Medicinrådets vurdering af ofatumumab til attakvis MS er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Novartis. Medicinrådet modtog ansøgningen den 14. juni 2021.

De kliniske spørgsmål er:

1. Hvilken værdi har ofatumumab sammenlignet med teriflunomid for voksne patienter med aktiv attakvis MS og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

2. Hvilken værdi har ofatumumab sammenlignet med ocrelizumab for voksne patienter med aktiv attakvis MS og høj sygdomsaktivitet (andenlinjebehandling)?

3.1 Attakvis multipel sklerose

Multipel sklerose (MS) er en kronisk inflammatorisk lidelse i centralnervesystemet, der typisk debuterer i 20-40 års alderen og rammer kvinder ca. dobbelt så ofte som mænd. I Danmark lever omkring 17.000 personer med MS, og den årlige incidens er ca. 600 [1,2].

MS er karakteriseret ved, at flere lokaliserede områder i hjerne og rygmarv angribes af immunologiske celler og komponenter, som ødelægger myelinskeder omkring nervefibrenes udløbere (aksoner). Tab af myelinskede forringer eller ødelægger aksonets evne til at transmittere elektriske signaler og medfører nedsat ledningshastighed eller ledningsblok resulterende i neurologiske udfald. Udover at være immunmedieret er sygdommens underliggende årsag ukendt. Der er dog fundet en række genetiske, miljømæssige og livsstilsassocierede risikofaktorer [3,4].

Patienter med MS vil opleve symptomer på deres sygdom, afhængigt af hvor deres læsion befinder sig i centralnervesystemet. Disse symptomer omfatter synspåvirkning, nedsat motorisk funktion, føleforstyrrelser, nedsat balance, vandladningsforstyrrelse, forstoppelse, nedsat seksualfunktion, smerter, træthed samt nedsat hukommelse og koncentrationsevne. Patienternes livskvalitet kan være meget negativt påvirket af symptomerne på deres sygdom.

MS kan inddeles i to overordnede kategorier: attakvis MS og progressiv MS. Attakvis MS er langt den hyppigste form for MS og er karakteriseret ved attakvise episoder med forværring af symptomer efterfulgt af perioder med bedring. Attakvis MS kan progrediere til sekundær progressiv MS (SPMS), hvor der ses et sygdomsforløb med progressiv forværring. MS kan også kategoriseres yderligere i forhold til, om sygdommen er aktiv eller ikke-aktiv [5,6]. Med aktivitet menes der attakker eller forværring, som ses på scanninger.

3.2 Ofatumumab

Ofatumumab (Kesimpta) er et fuldt humaniseret monoklonalt IgG_1 antistof, der binder specifikt til et molekyle, som kaldes CD20. CD20 er et overfladeprotein på B-celle-lymfocytter og i mindre grad på nogle T-celle-lymfocytter [7,8].

Ofatumumab virker som et B-celle-depleterende lægemiddel i lighed med andre monoklonale antistoffer rettet mod CD20, f.eks. rituximab og ocrelizumab.

Ofatumumab er tilgængeligt i form af en opløsning til subkutan injektion. Ofatumumab doseres med 20 mg om ugen de første tre uger. Herefter holdes en uges pause, før der overgås til månedlig dosering.

Ofatumumab er indiceret til behandling af voksne patienter med attakvise former for MS med aktiv sygdom defineret ved kliniske og/eller radiologiske undersøgelser. Indikationen omfatter nydiagnosticerede patienter med attakvis MS og patienter, der allerede er i behandling, men som skifter behandling pga. manglende effekt eller bivirkninger. Ofatumumabs indikation omfatter således både 1. og 2. linje i dansk behandlingspraksis inden for MS. Se mere i afsnit 3.3 Nuværende behandling.

3.3 Nuværende behandling

MS er en uhelbredelig sygdom, og i attakvis MS er det overordnede behandlingsformål at begrænse varighed og intensitet af det akutte attak, at symptomlindre samt at reducere frekvens og intensitet af fremtidige attakker. Derved håber man at kunne begrænse funktionstab og øge patientens livskvalitet. Behandling af attakvis MS kan således inddeles i to kategorier: symptomlindrende behandling og sygdomsmodificerende behandling (disease modifying therapy, DMT).

3.3.1 Inddeling af patienter

Lægemidler til behandling af attakvis MS er delt op i første og anden linje i Medicinrådets nuværende behandlingsvejledning Baggrund for Medicinrådets behandlingsvejledning vedr. attakvis multipel sklerose-vers. 1.2 (medicinraadet.dk) og lægemiddelrekommandation Medicinrådets lægemiddelrekom. og behandlingsvejl. vedr. attakvis multipel sklerose-vers. 1.4 (medicinraadet.dk) [9,10]. Dette skal forstås således, at de mest effektive og potentielt mest bivirkningstunge lægemidler kaldes andenlinjepræparater og forbeholdes patienter med størst sygdomsaktivitet eller patienter, hvor førstelinjebehandling viser sig ikke at være effektiv nok.

3.3.2 Førstelinjepræparater

Patienterne, som kan behandles med lægemidler fra gruppen af førstelinjepræparater, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret klinisk og radiologisk). Skift mellem lægemidler inden for gruppen af førstelinjepræparater kan ske på grund af eksempelvis betydende bivirkninger eller ændringer i graviditetsønske.

Patienter, som behandles med førstelinjepræparater, opdeles efter graviditetsønske og anvendelse af antikonception. Baggrunden for dette er, at der anbefales forskellige udvaskningsperioder for lægemidlerne inden påbegyndt graviditet. I den nuværende behandlingsvejledning er dimethylfumarat og teriflunomid klinisk ligestillede til mænd og kvinder, som benytter antikonception [10]. I lægemiddelrekommandationen er teriflunomid førstevalg for populationen "mænd og kvinder, som anvender antikonception og ikke har graviditetsønske" og dimethylfumarat for populationen "kvinder, som anvender antikonception og har graviditetsønske inden for ca. et år".

3.3.3 Andenlinjepræparater

Patienterne, som kan behandles med lægemidler fra gruppen af andenlinjepræparater [9], er:

- patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat
- patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet.

4. Metode

Medicinrådets protokol for vurdering vedrørende ofatumumab beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har ofatumumab sammenlignet med teriflunomid for voksne patienter med aktiv attakvis MS og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

5.1.1 Litteratur

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

Ansøgningen baserer sig på den artikel, der er angivet i protokollen:

Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020;383(6):546–5 [10]

I artiklen indgår de to identiske RCT'er ACSLEPIOS I & II, hvor ofatumumab testes over for teriflunomid i en MS-patientpopulation.

ASCLEPIOS består af to identiske fase III randomiserede og kontrollerede kliniske forsøg (ASCLEPIOS I & II). De kliniske forsøg var parallelle, dobbeltblindede, placebokontrollerede og med en aktiv komparator, som var teriflunomid. Her blev MS-patienter med enten attakvis MS (~95 %) eller sekundær progressiv MS med sygdomsaktivitet randomiseret 1:1 til 20 mg s.c. ofatumumab hver 4. uge (efter initialdosis) eller 14 mg teriflunomid dagligt i op til 30 måneder. Studiet er designet med en hierarkisk analyseplan, hvor det primære endepunkt er årlig attakrate. Sekundære endepunkter bestod bl.a. af sygdomsforværring (CDP-3), magnetisk resonansskanning og nye T2-læsioner. I alt blev 946 patienter randomiseret til ofatumumab og 936 til teriflunomid. Den mediane opfølgningstid var 1,6 år.

Ansøger har vedlagt *data on file* på endepunkterne kognitiv funktion og livskvalitet. Resultaterne stammer fra ASCLEPIOS I & II.

Disse data kan belyse effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data (Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser (medicinraadet.dk)) Data-on-file er fortrolige da ansøger endnu ikke har offentliggjort dem.

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population
Ofatumumab versus teriflunomide in multiple sclerosis. Hauser SL et al. N Engl J Med. 2020 [10]	ASCLEPIOS I, fase 3 randomiseret og kontrolleret dobbeltblindet studie. Median opfølgningstid: 1,6 år	NCT02792218	Klinisk spørgsmål 1 og 2
Ibid.	ASCLEPIOS II	NCT02792231	Klinisk spørgsmål 1 og 2

Som beskrevet i protokollen til vurdering af ofatumumab til behandling af attakvis MS udgør studiet af Hauser et al. (ASCLEPIOS I & II) et tilstrækkeligt datagrundlag sammen med EMAs EPAR [11] til at besvare klinisk spørgsmål 1.

Tabel 2. Baselinekarakteristika

	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (N = 465)	**Teriflunomid (N = 462)**	**Ofatumumab (N = 481)**	**Teriflunomid (N = 474)**
Alder, år	38,9 ± 8,8	37,8 ± 9,0	38,0 ± 9,3	38,2 ± 9,5
Kvinder, n (%)	318 (68,4)	317 (68,6)	319 (66,3)	319 (67,3)
Type af MS, n (%) Attakvis MS; Sekundær progressiv	438 (94,2); 27 (5,8)	434 (93,9); 28 (6,1)	452 (94,0); 29 (6,0)	450 (94,9); 24 (5,1)
Tid siden symptomdebut, år	8,36 ± 6,84	8,18 ± 7,21	8,20 ± 7,40	8,19 ± 7,38
Tid siden diagnose, år	5,77 ± 6,05	5,64 ± 6,20	5,59 ± 6,38	5,48 ± 6,00
Ingen tidligere sygdomsmodificerende behandling, n (%)	191 (41,1)	182 (39,4)	195 (40,5)	181 (38,2)
Tidligere sygdomsmodificerende behandling, n (%)				
Interferon beta	189 (40,6)	193 (41,8)	197 (41,0)	193 (40,7)
Glatirameracetat	124 (26,7)	106 (22,9)	118 (24,5)	149 (31,4)
Dimethylfumarat	36 (7,7)	37 (8,0)	36 (7,5)	44 (9,3)
Teriflunomid	8 (1,7)	6 (1,3)	13 (2,7)	9 (1,9)
Daclizumab	5 (1,1)	12 (2,6)	8 (1,7)	7 (1,5)
Fingolimod	10 (2,2)	15 (3,2)	13 (2,7)	10 (2,1)
Natalizumab	31 (6,7)	36 (7,8)	26 (5,4)	20 (4,2)
B-celleterapi	2 (0,4)	3 (0,6)	0	0
Laquinimod	5 (1,1)	4 (0,9)	2 (0,4)	7 (1,5)
Anden sygdomsmodificerende behandling	52 (11,2)	65 (14,1)	68 (14,1)	81 (17,1)
Antal relaps sidste 12 måneder	1,2 ± 0,6	1,3 ± 0,7	1,3 ± 0,7	1,3 ± 0,7
Antal relaps sidste > 12-24 måneder	0,9 ± 0,9	0,9 ± 1,2	0,7 ± 0,9	0,8 ± 1,0
EDSS-score	2,97 ± 1,36	2,94 ± 1,36	2,90 ± 1,34	2,86 ± 1,37
Antal af *gadolinium-enhancing lesions per T1-weighted MRI* scanning	1,7 ± 4,9	1,2 ± 2,6	1,6 ± 4,1	1,5 ± 4,1

Baselinekarakteristika er velbalanceret mellem studiearmene og med stor lighed i sygdomsbyrde for interventions – og komparatorarme i henholdsvis ASCLEPIOS I & II. Der indgår 5-6 % patienter med sekundær progressiv multipel sklerose i studiet. Det bidrager med noget usikkerhed, idet patienter med sekundær progressiv multipel sklerose ikke er en del af det kliniske spørgsmål fra Medicinrådets protokol til vurdering af ofatumumab til attakvis MS. Fagudvalget bemærker, at der er en stor andel af de behandlingserfarne patienter i ASCLEPIOS, der har modtaget injektionspræparater såsom interferon eller glatirameracetat ved tidligere behandling. Dette er ulig dansk klinisk praksis, hvor kun et fåtal af patienterne i dag behandles med interferoner eller glatirameracetat. Derudover er der væsentligt færre patienter, som har modtaget teriflunomid og dimethylfumarat i studiepopulationen end i dansk klinisk praksis [12]. B-celledepleterende behandling inden for de sidste to år er et eksklusionskriterium i ASCLEPIOS og antallet af patienter, der har modtaget B-celledepleterende behandling, er også meget lavt i ASCLEPIOS ift. den danske population af MS-patienter. Her er det ca. 15 % af patienterne i sygdomsmodificerende behandling, der modtager B-celledepleterende behandling (ocrelizumab eller rituximab), dvs. at der er flere væsentlige forskelle mellem studiepopulationen i ACSLEPIOS og den danske population af MS ift. tidligere modtaget behandling. Hvilken betydning det har for overførbarheden af studiets resultater er svært at forudsige.

Gennemsnitsalderen i ASCLEPIOS var ca. 38 år, hvilket er noget lavere end medianalderen i den danske population af MS-patienter, hvor medianalderen er 50-59 år [12]. Dog matcher de 38 år meget godt med medianalderen for behandlingsnaive danske patienter. I ASCLEPIOS var patienterne over 55 år eller med en EDSS-score over 5,5 ekskluderet fra deltagelse. Denne population udgør en betydelig del af den danske MS-patientpopulation. Generelt forventes en yngre patientpopulation at kunne tolerere og evt. respondere bedre på behandling end en ældre patientpopulation.

Tabel 3. Danske MS-patienter i aktuel sygdomsmodificerende behandling, 2021 [12]

Behandling	Antal	Procent
Dimethylfumarat	1.586	18,4
Teriflunomid	1.572	18,2
Fingolimod	1.314	15,2
Ocrelizumab	1.111	12,9
Natalizumab	1.058	12,3
Interferon beta	887	10,3
Glatirameracetat	417	4,8
Cladribin	212	2,5
Alemtuzumab	149	1,7
Anden behandling	313	3,8

5.1.2 Databehandling og analyse

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

Ansøger har indsendt et datagrundlag, der er i overensstemmelse med Medicinrådets protokol, og dataanalyserne er beskrevet tilstrækkeligt og udført hensigtsmæssigt. Der indgår data på alle ønskede effektmål. Effektdata er baseret på ITT-populationen i ASCLEPIOS, og sikkerhedsdata er baseret på sikkerhedspopulationen.

På effektmålet årlig attakrate er attakraten justeret på baggrund af en negativ binomialfordeling med en log-link funktion, hvori kovariater for studiepopulationen og historisk attakrate indgår. Dette er beskrevet i det kliniske studie af lægemidlet [10]. Medicinrådet accepterer denne tilgang.

I protokollen til vurdering af ofatumumab til attakvis MS efterspurgte Medicinrådet resultater for endemålet livskvalitet på det sygdomsspecifikke mål for livskvalitet MSQOL-54. Ansøger har ikke kunnet levere MSQOL-54-data, men i stedet rapporteret livskvalitet med det generiske mål EQ-5D-5L. Medicinrådet accepterer denne tilgang.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen for klinisk **spørgsmål 1**. 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).

Der er nedgraderet for indirekthed på alle effektmål, da populationen i studiet adskiller sig fra patienter i dansk klinisk praksis ved bl.a. at være mere behandlingsnaive og have modtaget anden sygdomsmodificerende terapi end patienter modtager i dansk klinisk praksis. På enkelte effektmål er der nedgraderet for unøjagtighed, da der var brede konfidensintervaller. Den laveste evidenskvalitet for et kritisk effektmål er ”meget lav”, hvilket bliver den samlede konklusion.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias er lav.

Når evidensens kvalitet er meget lav, betyder det, at nye studier med meget høj sandsynlighed kan ændre konklusionen.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.1.4 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 4. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Vedvarende sygdomsforværring bekræftet efter 3 måneder (CDP3)	Andel patienter med en ændring i CDP bekræftet efter 3 mdr. (10 %-point)	Kritisk	-4,90 %-point (95 % CI: -7,20; -1,98)	Ingen dokumenteret merværdi	0,655 (95 % CI: 0,500; 0,858)	Moderat merværdi	Moderat merværdi for den relative effektforskel
Bivirkninger	Andel patienter, der oplever en eller flere alvorlige bivirkninger (3 %-point) Suppleret med kvalitativ gennemgang af bivirkningsprofil (kvalitativ vurdering)	Kritisk	1,1 %-point (95 % CI: -1,4; 3,6)	Ingen dokumenteret merværdi	1,151 (95 % CI: 0,855; 1,550)	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
Årlig attakrate	Antal attakker pr. patient om året (0,1 attakker pr. patient pr. år)	Vigtig	-0,128 årlig attakrate (95 % CI: -0,163; -0,093)	Ingen dokumenteret merværdi	ASCLEPIOS I: RR 0,49 (95 % CI: 0,37; 0,65) ASCLEPIOS II: RR 0,42 (95 % CI: 0,31; 0,56)	Moderat merværdi	Moderat merværdi for den relative effektforskel
Kognitiv funktion	Andel patienter, som undgår en 10 %-points forværring på SDMT (10 %-point)	Vigtig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

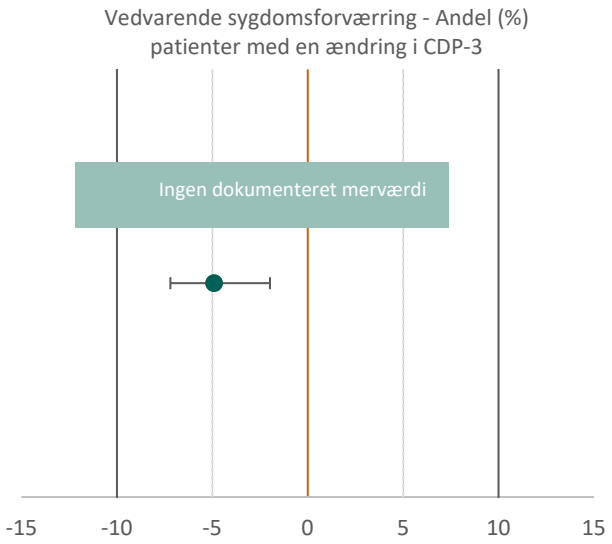
Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Livskvalitet	Gennemsnitlig ændring i MSQOL54 (0,5 SD)	Vigtig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Konklusion	Fagudvalget vurderer, at ofatumumab samlet ikke kan kategoriseres efter Medicinrådets metoder. Hvis man udelukkende tager udgangspunkt i de relative effektforskelle har ofatumumab en moderat merværdi.til patienter med gennemsnitlig sygdomsaktivitet sammenlignet med teriflunomid på effektmålene vedvarende sygdomsforværring og attakrate.						
Kvalitet af den samlede evidens		Meget lav					

CI = Konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = Relativ risiko.

Vedvarende sygdomsforværring
Som beskrevet i protokollen er effektmålet sygdomsforværring kritisk for vurderingen af lægemidlets værdi, fordi et centralt mål med behandlingen er at forsinke progression af sygdommen og forværring af symptomer. Effektmålet dækker over andelen af patienter, der oplever vedvarende sygdomsforværring, og derfor er en positiv ændring i andelen et negativt resultat for patienterne.

Medicinrådet har i protokollen til vurdering af ofatumumab til behandling af attakvis MS anmodet om længst muligt opfølgningstid. Ansøger har vedlagt effektestimater på effektmålet vedvarende sygdomsforværring, som er opgjort efter 2 år. Omtrent 2/3 af patientpopulationen er blevet censureret ved 2 år. Det medfører, at effektestimatet er behæftet med en betydelig usikkerhed.

I ASCLEPIOS I havde 11,3 % af patienterne behandlet med ofatumumab en vedvarende sygdomsforværring, som blev bevaret over 3 måneder ved 2 års **opfølgningstid**, hvilket var tilfældet for 15,4 % patienterne i komparatorarmen. Tilsvarende var det 10,5 % og 14,6 % for henholdsvis ofatumumab og teriflunomid i ACLEPIOS II.



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for vedvarende sygdomsforværring. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 1 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har ofatumumab foreløbigt **ingen dokumenteret merværdi** vedr. vedvarende sygdomsforværring.

Baseret på den relative effektforskel, som fremgår af tabel 4, (RR: 0,66 (0,50; 0,86) har ofatumumab en **moderat merværdi** vedr. vedvarende sygdomsforværring.

Fagudvalget vurderer, at ofatumumab samlet set har en moderat merværdi vedr. vedvarende sygdomsforværringer ift. de relative effektmål. Dermed ser fagudvalget bort fra, at den mindste klinisk relevante forskel på den absolutte effektforskel ikke er opnået. Det gør fagudvalget, fordi andelen af patienter, der får en vedvarende sygdomsforværring i komparatorarmen, er meget lav (~15 %), og muligheden for at opnå en forskel på 10 %-point ved behandling med ofatumumab er uforholdsvis svær at opnå. Dette ville indebære, at risikoen for vedvarende sygdomsforværring skulle reduceres til mindre end 5 %. Fagudvalget bemærker, at en signifikant forskel på 4,9 %-point i, hvor stor en andel patienter der oplever en vedvarende sygdomsforværring efter 2 års opfølgningstid, er et markant resultat inden for behandling af attakvis MS.

Fagudvalget argumenterer yderligere med, at de antager, at ofatumumabs effekt på at bremse den vedvarende sygdomsforværring akkumuleres henover behandlingsperioden, og at effekten derfor vil have en markant klinisk relevans for patienter med attakvis MS.

Bivirkninger
Som beskrevet i protokollen er effektmålet bivirkninger et kritisk effektmål, da det belyser, hvor godt patienterne tolererer ofatumumab sammenlignet med komparator. Samtidig kan patienterne være præget af mange alvorlige symptomer på deres sygdom. Fagudvalget ønskede både en kvantitativ opgørelse opgjort som antal patienter, der oplevede en eller flere alvorlige bivirkninger, og en kvalitativ gennemgang af ofatumumabs bivirkningsprofil.

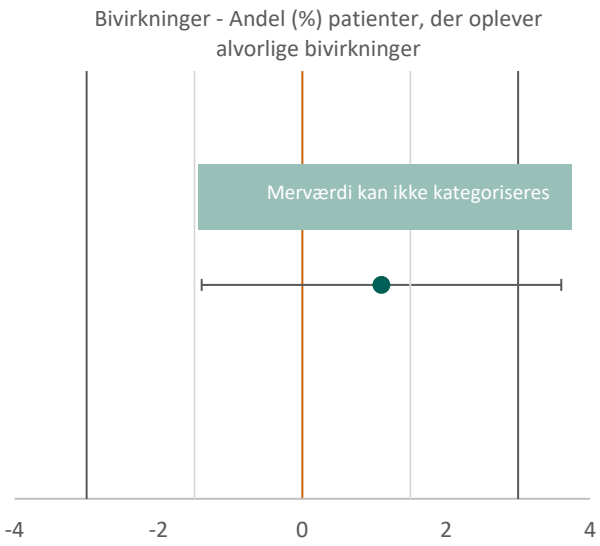
Ansøger har ikke indsendt data for alvorlige bivirkninger, men for alvorlige uønskede hændelser. Medicinrådet accepterer denne tilgang, men understreger, at det bidrager til usikkerhed vedr. opgørelsen over bivirkninger.

Alvorlige bivirkninger
Medicinrådet finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever én eller flere alvorlige bivirkninger, er relevant for vurderingen. Da der allerede eksisterer flere effektive behandlingsalternativer, vil fagudvalget ikke acceptere, at en ny behandling er markant mere bivirkningstung.

Ansøger har opgjort tal for alvorlige uønskede hændelser:

I ASCLEPIOS I oplevede 10,3 % af patienterne behandlet med ofatumumab en alvorlig uønsket hændelse, hvilket var tilfældet for 8,2 % patienterne i komparatorarmen behandlet med teriflunomid. Tilsvarende var det 7,9 % og 7,6 % for henholdsvis ofatumumab og teriflunomid i ACLEPIOS II.

Af EMAs EPAR fremgår det, at de hyppigst rapporterede alvorlige uønskede hændelser ved behandling med ofatumumab var følgende: infektioner (2,5 %), traumer, forgiftninger og behandlingskomplikationer (1,4 %), psykiatriske lidelser (1,1 %) og godartede tumorer, ondartede og uspecificerede (herunder cyster og polypper) (1,0 %). Andelen af patienter, der afbrød behandling på grund af en alvorlig uønsket hændelse, var for ofatumumab 11 patienter (1,2 %) og for teriflunomid 8 patienter (0,8 %).



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel af patienter, der oplever alvorlige bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 2 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. 95 % konfidensintervallet omfatter både positive og negative værdier. Derfor kan den foreløbige værdi af ofatumumab vedr. patienter, der oplever alvorlige bivirkninger, **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 4, RR: 1,15 (95 % CI: 0,865; 1,56) kan værdien af ofatumumab foreløbigt **ikke kategoriseres** vedr. alvorlige bivirkninger.

Kvalitativ gennemgang af bivirkningsprofil

Medicinrådet har ønsket en gennemgang af ofatumumabs bivirkningsprofil med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Medicinrådet ønsker sikkerhedsdata på langtidseffekter (≥ 5 år) ved behandling med ofatumumab. Herunder ønskes bivirkninger angivet med særligt fokus på udvikling af neutropeni, faldende IgG-niveauer, infektioner og vaccinationsrespons.

Tabel 5. Sikkerhedsresultater for ASCLEPIOS I & II

	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (N = 465)	Teriflunomid (N = 462)	Ofatumumab (N = 481)	Teriflunomid (N = 474)
Alle uønskede hændelser	382 (82,2)	380 (82,3)	409 (85,0)	408 (86,1)
Uønskede hændelser, der fører til behandlingsophør	27 (5,8)	24 (5,2)	27 (5,6)	25 (5,3)
Infektion	229 (49,2)	238 (51,5)	259 (53,8)	255 (53,8)
Injektionsrelateret systemisk reaktion	75 (16,1)	76 (16,5)	116 (24,1)	64 (13,5)
Alvorlig uønsket hændelse	48 (10,3)	38 (8,2)	38 (7,9)	36 (7,6)
Alvorlig infektion	12 (2,6)	7 (1,5)	12 (2,5)	10 (2,1)
Alvorlig injektions-relateret reaktion	2 (0,4)	0	0	0
Neoplasi	3 (0,6)	3 (0,6)	2 (0,4)	1 (0,2)
Død	0	0	0	1 (0,2)

Uønskede hændelser af særlig interesse

Ifølge EMAs EPAR vurderes de mest centrale sikkerhedsrisici ved behandling med ofatumumab at være risikoen for injektionsrelaterede reaktioner og en øget infektionsrisiko. Dette er i lighed med andre CD20-depleterende lægemidler. Heraf kommer også risikoen for et nedsat vaccinationsrespons på levende eller svækkede vacciner med en efterfølgende risiko for infektion. I EMAs EPAR vurderes det, at klinisk relevante uønskede hændelser såsom injektionsrelaterede reaktioner, øvre luftvejsinfektioner, urinvejsinfektioner, herpes – eller varicella-zoster virusinfektioner – var hyppigere i ofatumumab-armen end i komparatorarmen i sikkerhedsdatasættet [11].

De hyppigst rapporterede infektioner omfattede, men var ikke begrænset til: nasopharyngitis (18,0 %), øvre luftvejsinfektioner (10,3 %), urinvejsinfektioner (10,3 %) og influenza (6,6 %).

Øget kræftrisiko er kendt fra andre immunmodulerende lægemidler. F.eks.er brystkræft inkluderet som en uønsket hændelse ved behandling med ocrelizumab og på samme måde hudkræft for sphingosine-1-fosfat-modulatorerne, hvor især fingolimod er benyttet i dansk klinisk praksis. Det data, der foreligger i denne ansøgning, kan ikke afvise, at en lignende risiko gælder ved langtidsbehandling med ofatumumab. Kræftrisiko er beskrevet i ofatumumabs *risk management plan* (RMP) til EMA, og aktive maligniteter er inkluderet som en kontraindikation i ofatumumabs SmPC.

Idet den mediane opfølgningstid i studiet var 1,6 år mener fagudvalget ikke, at datagrundlaget kan sige noget om langtidsbivirkningerne ved ofatumumab. Ansøger skriver, at data fra et open-label follow-up-studie, ALITHIOS, viser, at infektionsrisikoen ved 3,5 år er konsistent med, hvad der er rapporteret i ASCLEPIOS I & II. Fagudvalget vurderer, at der på nuværende tidspunkt er en usikkerhed omkring bivirkninger ved langtidsbehandling med ofatumumab.

Konklusion angående bivirkninger
Fagudvalget finder det ikke dokumenteret ud fra det indleverede datagrundlag, at der er en afgørende forskel mellem ofatumumab og teriflunomid angående sikkerhed.

Fagudvalget har et stort kendskab og lang erfaring i at behandle med teriflunomid, hvor bivirkningsprofilen og monitorering er håndterbar i klinisk praksis. Mht. ofatumumab er fagudvalget bekymret for alvorlige langtidsbivirkninger (heriblandt late-onset neutropeni, opportunistiske infektioner, reduceret vaccinerespons og faldende IgG-niveauer), som ikke er tilstrækkeligt belyst i de foreliggende studier pga. den begrænsede opfølgningstid.

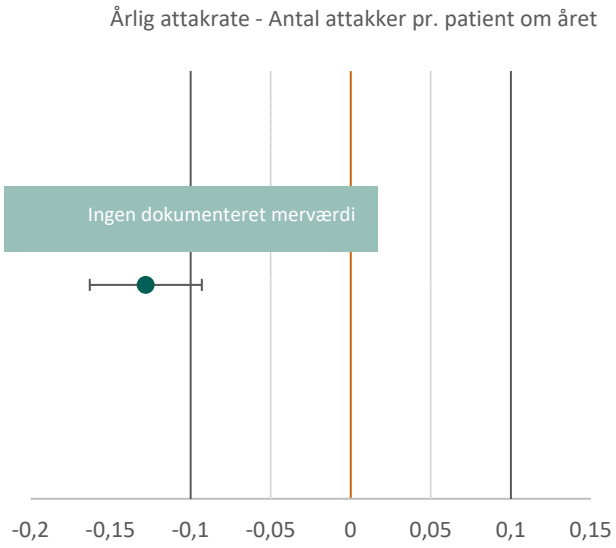
Fagudvalget vurderer, at ofatumumab **ingen dokumenteret værdi** har vedr. bivirkninger, men tager forbehold for væsentlige usikkerheder, hvad angår langtidsbivirkninger ved behandlingen, som fylder meget i den konkrete kliniske vurdering af patientens behandlingsmuligheder.

Årlig attakrate
Som beskrevet i protokollen er effektmålet årlig attakrate vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi attakker ofte medfører varige funktionstab hos patienter med attakvis MS. Effektmålet dækker over antal attakker pr. år, hvorved en positiv ændring er et negativt resultat for patienterne.

I ASCLEPIOS I var årlig attakrate 0,11 (95 % CI 0,09; 0,14) for ofatumumab og 0,22 (95 % CI 0,18; 0,26) for teriflunomid, hvilket resulterede i en estimeret absolut forskel på -0,11 (95 % CI -0,16; -0,06) og en estimeret relativ forskel på 0,49 (95 % CI 0,37; 0,65).

I ASCLEPIOS II var årlig attakrate 0,10 (95 % CI 0,08; 0,13) for ofatumumab og 0,25 (95 % CI 0,21; 0,3) for teriflunomid, hvilket resulterede i en estimeret absolut forskel på -0,15 (95 % CI -0,2; -0,09) og en estimeret relativ forskel på 0,42 (95 % CI 0,31; 0,56).

Fagudvalget bemærker, at den årlige attakrate inden randomisering ca. er 1,3 attakker pr. år for samtlige patienter i begge studier (se tabel 4), mens den i ASCLEPIOS-studiet falder til henholdsvis 0,11 og 0,22. Det er en meget stor forskel i attakrate før og efter studiestart. Den årlige attakrate er justeret på baggrund af en negativ binomialfordeling med en log-link-funktion for bedre at kunne prediktere attakraten i subpopulationer i studiet. I og med at den historiske attakrate indgår i denne justering, antager fagudvalget, at usikkerheden på den historiske attakrate kan påvirke effektestimatet på den justerede årlige attakrate. Det antages dog at være fordelt jævnt på begge arme i studiet, så usikkerheden på forskellen i attakrate er lille.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for årlig attakrate. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 3 ovenfor.

Punktestimatet for den absolutte effektforskel er fremkommet ved en simpel metaanalyse af begge studier (ASCLEPIOS I & II) og afspejler en klinisk relevant effektforskel på -0,128 attakker pr. år, men den øvre grænse for konfidensintervallet er større end den klinisk relevante forskel. Derfor er den foreløbige værdi af ofatumumab **ingen dokumenteret merværdi** vedr. årlig attakrate.

Ansøger har ikke indsendt et estimat fra en metaanalyse for den relative effektforskel på den justerede årlige attakrate for ASCLEPIOS I & II for begge studier.

Baseret på de relative risici på 0,49 (95 % CI: 0,37; 0,65) og 0,42 (95 % CI: 0,31; 0,56) har ofatumumab foreløbigt en **moderat merværdi** vedr. årlig attakrate.

Fagudvalget vurderer, at ofatumumab samlet set har en **moderat merværdi** vedr. årlig attakrate ift. de relative effektmål. Det gør fagudvalget, fordi attakraten er meget lille i komparatorarmen i ASCLEPIOS (0,22; 0,25), og derved er det uforholdsmæssigt svært at opnå en statistisk signifikant gennemsnitlig forskel på 0,1 attak/år.

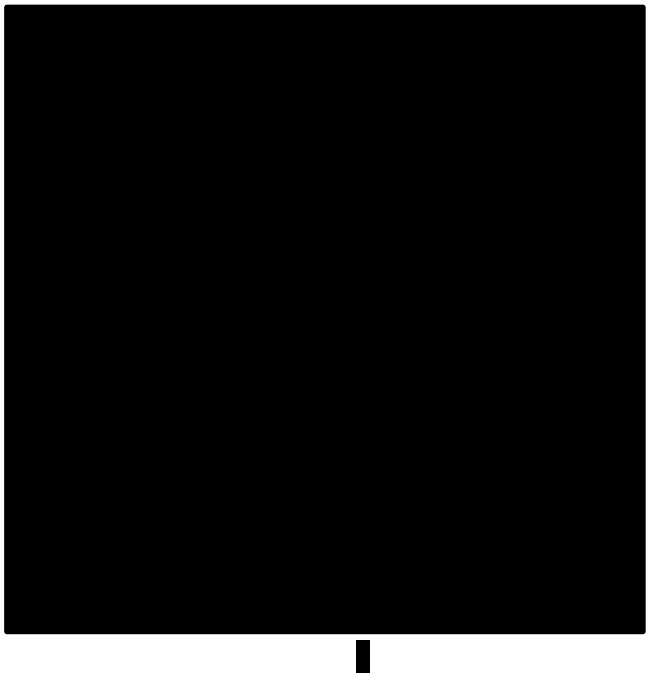
Fagudvalget mener endvidere, at ofatumumabs effekt på årlig attakrate akkumuleres henover behandlingsperioden, og at effekten derfor vil have en markant klinisk relevans for patienter med attakvis MS, idet det er en kronisk sygdom med livslang behandling.

Kognitiv funktion
Som beskrevet i protokollen er effektmålet kognitiv funktion vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes kognitive funktion har stor

betydning for patienternes trivsel og funktionsniveau. Ansøger har vedlagt resultater for effektmålet kognitiv funktion som *data on file.*

[redacted]

[redacted]



[redacted]

Den absolutte forskel er vist i figur 4 ovenfor.

[redacted]

[redacted].

Fagudvalget vurderer, at ofatumumab samlet set **ingen dokumenteret merværdi** har vedr. kognitiv funktion.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes livskvalitet selvsagt har stor betydning for lægemidlets umiddelbare værdi for patienterne. Ansøger har vedlagt resultater for effektmålet livskvalitet som *data on file* og med det generiske EQ-5D-5L-livskvalitetsværktøj efter 96 ugers opfølgning.

[redacted]

Fagudvalget vurderer, at ofatumumab aggregeret ingen dokumenteret merværdi har vedr. livskvalitet.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at patienterne i det kliniske studie er fulgt i for kort tid til at dokumentere om ofatumumab kan forsinke, at sygdommen udvikler sig på længere sigt. Data indikerer dog, at ofatumumab kan være et mere effektivt lægemiddel end teriflunomid. Ofatumumab har en moderat merværdi på de relative effektforskelle for vedvarende sygdomsforværring og attakrate, men de absolutte effektforskelle overstiger ikke de mindste klinisk relevante forskelle. Derfor vurderer fagudvalget, at værdien af ofatumumab til patienter med gennemsnitlig sygdomsaktivitet ikke kan kategoriseres efter Medicinrådets metoder sammenlignet med teriflunomid.

Det er pga. usikkerhed omkring balancen mellem effekt og risiko for langsigtede alvorlige bivirkninger for gruppen af patienter med gennemsnitlig sygdomsaktivitet, at fagudvalget ikke kan kategorisere lægemidlets værdi.

Fagudvalget mener, at **ofatumumab ikke er relevant som førstelinjebehandling** i fagudvalgets nuværende behandlingsalgoritme (se afsnit 3.3) til patienter med attakvis MS grundet bekymring for langsigtede og alvorlige bivirkninger.

5.2 Klinisk spørgsmål 2

Hvilken værdi har ofatumumab sammenlignet med ocrelizumab for voksne patienter med aktiv attakvis MS og høj sygdomsaktivitet (andenlinjebehandling)?

5.2.1 Litteratur

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

Der findes ikke studier, hvor ofatumumab er direkte sammenlignet med ocrelizumab. Derfor har Medicinrådet angivet en søgestreng i protokollen, så ansøger kunne finde studier til en indirekte sammenligning. Ansøger har søgt litteratur med søgestrengen og udvalgt to fuldtekstartikler.

Besvarelsen på klinisk spørgsmål 2 baserer sig på den artikel, der er angivet i protokollen til besvarelse af klinisk spørgsmål 1, samt registreringsstudiet for ocrelizumab. Ansøger har derudover indsendt upublicerede *data on file* fra ASCLEPIOS-studiet.

Disse data kan belyse effektmålene i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data (Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser (medicinraadet.dk)

Tabel 6. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population
Ofatumumab versus teriflunomide in multiple sclerosis. Hauser SL et al. N Engl J Med. 2020 [10]	ASCLEPIOS I	NCT02792218	Klinisk spørgsmål 1 og 2
Ibid.	ASCLEPIOS II	NCT02792231	Klinisk spørgsmål 1 og 2
Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. Hauser SL et al. N Engl J Med. 2017	OPERA I	NCT01247324	Klinisk spørgsmål 2
Ibid.	OPERA II	NCT01412333	Klinisk spørgsmål 2

ASCLEPIOS og OPERA er fase III registreringsstudier for henholdsvis ofatumumab og ocrelizumab. Studierne er randomiserede kontrollerede forsøg af høj kvalitet med ens inklusions- og eksklusionskriterier, men af forskellig varighed. OPERA varede i 96 uger, mens varigheden af ASCLEPIOS blev justeret på baggrund af en prædefineret

hændelsesrate, der resulterede i en median opfølgningstid på 1,6 år. De prædefinerede hændelsesrater var opnået, når følgende konditioner var opfyldt:

- Hvert forsøg havde opsamlet nok data til at kunne detektere med 90 % power en 40 %'s behandlingseffekt på årlig attakrate.
- Begge forsøg tilsammen havde opsamlet nok data til at kunne detektere med 90 % power en 38,6 %'s relativ reduktion i vedvarende sygdomsforværring efter 3 mdr. (CDW-3).
- Begge forsøg tilsammen havde opsamlet nok data til at kunne detektere med 80 % power en 38,6 %'s relativ reduktion i vedvarende sygdomsforværring efter 6 mdr. (CDW-6).

Patientpopulationerne er forskellige i ASCLEPIOS og OPERA (se baselinekarakteristika), hvilket påvirker sammenligneligheden af effektmålet på tværs af studierne negativt.

Tabel 7. Baselinekarakteristika

Baseline karakteristika	ASCLEPIOS I		ASCLEPIOS II		OPERA I		OPERA II	
Intervention	Ofatumumab 20 mg subkutant hver 4. uge, efter 20 mg loading dosis ved dag 1, 7 og 14				Ocrelizumab 600 mg intravenøst hver 24 uge			
Komparator	Teriflunomid 14 mg peroralt dagligt				Interferon beta-1a (Rebif) 44 µg subkutant tre gange ugentligt			
Design	RCT				RCT			
Primære endepunkt	ARR				ARR			
Alder	18-55 år				18-55 år			
Type af MS	Attakvis MS eller SPMS med sygdomsaktivitet				MS, ikke PPMS			
Opfølgningstid	Justeret på basis af en foruddefineret samlet minimumshændelsesrate. Median opfølgning var 1,6 år. Mere end 30 % af patienterne deltog i undersøgelsen i mere end 2 år.				96 uger			
Baseline k	**ASCLEPIOS I**		**ASCLEPIOS II**		**OPERA I**		**OPERA II**	
	OFA	TER	OFA	TER	OCR	INF	OCR	INF
N	465	462	481	474	410	411	417	418
Alder, gennemsnit (år)	38,9 ± 8,8	37,8 ± 9,0	38,0 ± 9,3	38,2 ± 9,7	37,1 ± 9,3	36,9 ± 9,3	37,2 ± 9,1	37,4 ± 9,0
Kvinder (%)	68,4	68,6	66,3	67,3	65,9	66,2	65,0	67,0
Varighed af MS siden diagnose (år)	5,77 ± 6,05	5,64 ± 6,20	5,59 ± 6,38	5,48 ± 6,00	3,82 ± 4,80	3,71 ± 4,63	4,15 ± 4,95	4,13 ± 5,07
Tidligere sygdomsmodificerende behandling (% med behandlingserfaring[a])	58,9	60,6	59,5	61,8	26,2	28,6	27,1	24,7
Antal attakker sidste 12 måneder	1,2 ± 0,6	1,3 ± 0,7	1,3 ± 0,7	1,3 ± 0,7	1,31 ± 0,65	1,33 ± 0,64	1,32 ± 0,69	1,34 ± 0,73
Baseline EDSS-score	2,97 ± 1,36	2,94 ± 1,36	2,90 ± 1,34	2,86 ± 1,37	2,86 ± 1,24	2,75 ± 1,29	2,78 ± 1,30	2,84 ± 1,38
Fravær af Gd+ T1 læsioner (%)	62,6	63,4	56,1	61,4	57,5	61,9	61,0	58,6

OFA = ofatumumab, TER = teriflunomide, OCR = ocrelizumab, INF = Interferon beta-1a.
[a]For OPERA I & II, referer specifikt til erfaring med hvilken som helst sygdomsmodificerende behandling to år op til screening.
Forkortelser: EDSS = Expanded Disability Status Scale; Gd+ = Gadolinium-enhancing; MS = Multipel Sclerosis; SPMS: S*econdary Progressive Multiple Sclerosis*; PPMS: *Primary Progressive Multiple Sclerosis.*

Baselinekarakteristika
ASCLEPIOS- og OPERA-studierne er internt velbalancerede på deres respektive interventions- og komparatorarme, men sammenlignes de mod hinanden, er der en række forskelle på tværs af studierne.

I ASCLEPIOS har patienterne gennemgående haft en MS-diagnose i 1-2 år længere end i OPERA-studierne. Det afspejles i mindre grad i patienternes EDSS-score ved baseline. Her er den kun marginalt højere i ASCLEPIOS. Generelt fremgår det dog, at patienterne i ASCLEPIOS har en lidt større sygdomsbyrde end patienterne i OPERA-studierne.

En væsentlig forskel er tidligere modtaget behandling, hvor det kun er ca. 26 % i OPERA, der har modtaget sygdomsmodificerende behandling. Til sammenligning er det ca. 60 % i ASCLEPIOS. Umiddelbart må det forventes, at behandlingsnaive patienter har et bedre udgangspunkt for at respondere på sygdomsmodificerende behandling end behandlingserfarne patienter. Den sygdomsmodificerende behandling, patienterne modtog i henholdsvis ASCLEPIOS og OPERA, er også forskellig, og i OPERA-studierne har patienterne nærmest udelukkende modtaget interferoner eller glatirameracetat.

Derudover er der en betydelig forskel i komparatorarmene i henholdsvis ASCLEPIOS og OPERA, hvor komparator i OPERA er interferon beta-1a, som forventes at have en væsentlig tungere bivirkningsprofil end teriflunomid, som er komparator i ASCLEPIOS. Effekten af teriflunomid og interferon beta-1a vurderer fagudvalget dog at være nogenlunde ligeværdig. Effekten af teriflunomid og interferon beta-1a er også ligestillet i behandlingsvejledningen for attakvis multipel sklerose [9].

For begge studier er der de samme forskelle til patienterne i dansk klinisk praksis som tidligere omtalt i afsnit 5.1.1.

5.2.2 Databehandling og analyse

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

Ansøger har indsendt en kvalitativ sammenligning af ofatumumab og ocrelizumab på baggrund af ASCLEPIOS I & II (ofatumumab vs. teriflunomid) og OPERA I & II (ocrelizumab vs. interferon beta-1a). Ansøger har valgt denne tilgang, da der ikke var en fælles komparator i studierne til at foretage en indirekte analyse vha. Bucher's metode. Medicinrådet accepterer valget af metode. Effektdata er baseret på ITT-populationen, og sikkerhedsdata er baseret på sikkerhedspopulationen til de respektive studier.

5.2.3 Evidensens kvalitet

Da vurderingen af ofatumumab er baseret på en kvalitativ sammenligning med ocrelizumab, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias er lav.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.2.4 Effektestimater og kategorier

Tabel 8. Effektmålsoversigt for ASCLEPIOS og OPERA

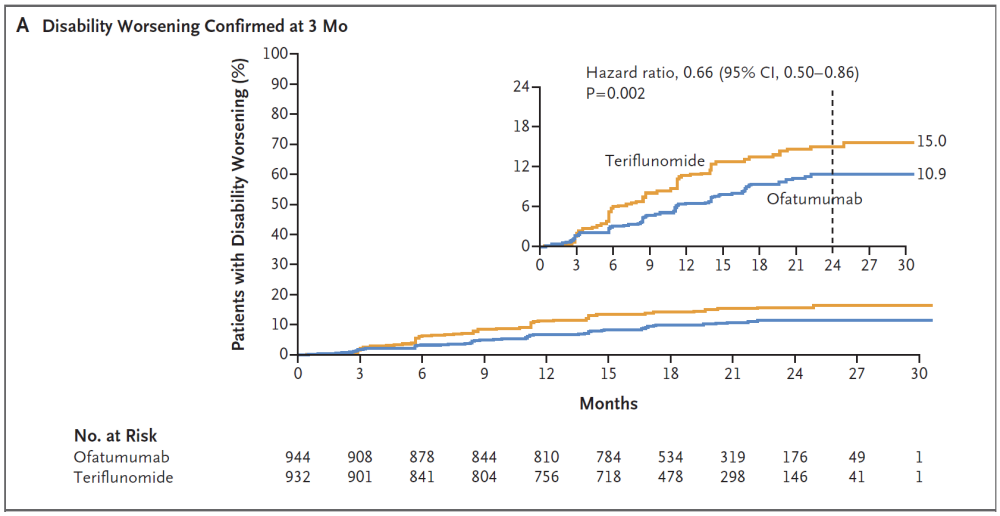
Resultater pr. endemål:	Studier inkluderet i analysen	Absolut effektforskel			Relativ effektforskel		
		Forskel	CI	*P* værdi	Forskel	CI	*P* værdi
CDW-3, % af patienter	ASCLEPIOS I & ASCLEPIOS II	-4,90	-7,20; -1,98	NA	0,655	0,500;0,858	0,0021
CDP-3, % af patienter	OPERA I & OPERA II	NA	NA	NA	0,603	0,449;0,809	0,0007
Alvorlige uønskede hændelser, % af patienter	ASCLEPIOS I & ASCLEPIOS II	1,116	-1,394; 3,625	NA	1,151	0,855;1,550	0,355
Alvorlige uønskede hændelser, % af patienter	OPERA I & OPERA II	-1,763	-4,346; 0,820	NA	0,793	0,567;1,107	0,173
Årlig attakrate	ASCLEPIOS I & ASCLEPIOS II	-0,128	-0,163; -0,093	<0,0001	NA	NA	NA
Årlig attakrate	OPERA I & OPERA II	-0,136	-0,188; -0,083	<0,0001	NA	NA	NA
SDMT, % af patienter uden 4 points forværring	ASCLEPIOS I & ASCLEPIOS II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SDMT, % af patienter uden 4 points forværring	OPERA I & OPERA II	NA	NA	NA	NA	NA	NA
EQ-5D utility score, gennemsnitlig ændring, uge 96	ASCLEPIOS I & ASCLEPIOS II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 fysisk komponent samlet score, gennemsnitlig ændring fra baseline til uge 96	OPERA I & OPERA II	0,929	0,021; 1,837	0,0449	NA	NA	NA

Vedvarende sygdomsforværring
Som beskrevet i protokollen er effektmålet sygdomsforværring kritisk for vurderingen af lægemidlets værdi, fordi et centralt mål med behandlingen er at forsinke progression af sygdommen og forværring af symptomer. Effektmålet dækker over andelen af patienter, der oplever vedvarende sygdomsforværring, og derfor er en positiv ændring i andelen et negativt resultat for patienterne.

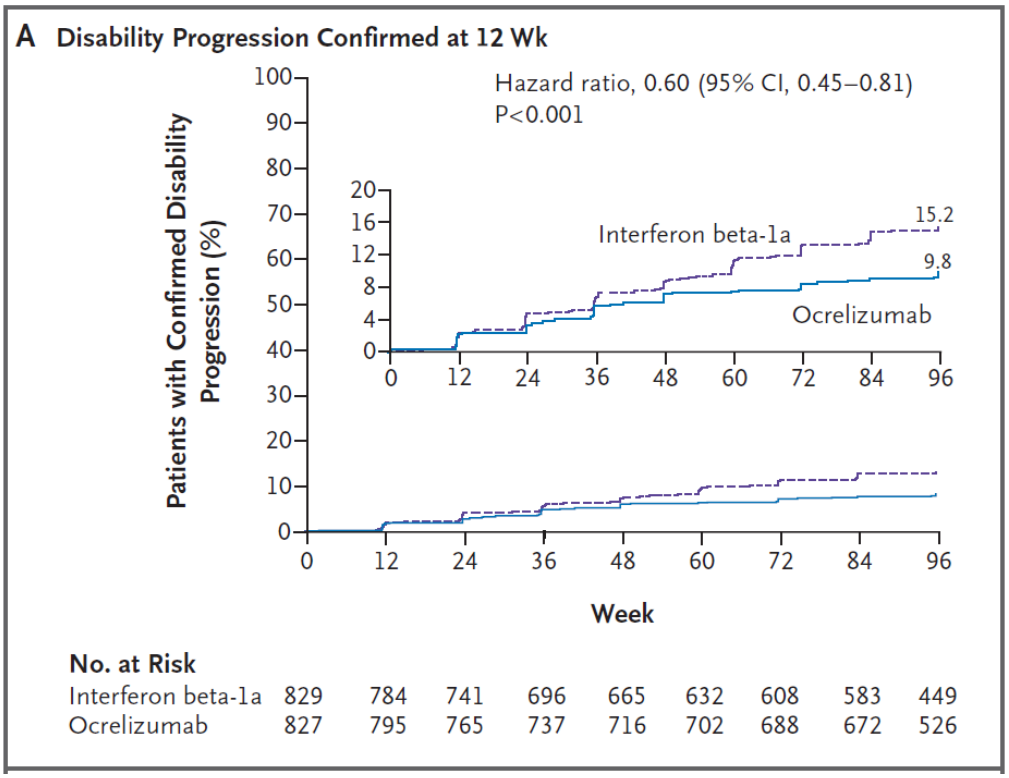
Se afsnit 5.1.4 for beskrivelse af effektdata på ofatumumab fra ASCLEPIOS, og se figur 5 og 6 med Kaplan-Meier-estimater på vedvarende sygdomsforværring i henholdsvis ASCLEPIOS- og OPERA-studierne. I OPERA og ASCLEPIOS er definitionen af effektmålet vedvarende sygdomsforværring ikke ens, hvilket bidrager med usikkerhed til den kvalitative sammenligning. Derudover gælder det, at 2/3 af patientpopulationen er blevet censureret ved 2 år.

I OPERA I var andelen af patienter med CDP-3 for ocrelizumab 7,6 % og 12,2 % for interferon-beta 1a, hvilket resulterede i en estimeret absolut forskel på -5,05 %-point (95 % CI -7,50; -1,15) og en estimeret relativ forskel på 0,57 (95 % CI 0,37; 0,90).

I OPERA II var andelen af patienter med CDP-3 for ocrelizumab 10,6 % og 15,1 % for interferon-beta 1a, hvilket resulterede i en estimeret absolut forskel på -5,3 % point (95 % CI -8,46; -1,12) og en estimeret relativ forskel på 0,63 (95 % CI 0,42; 0,92).



Figur 5. Kaplan-Meier-plot for effektmålet vedvarende sygdomsforværring (Hauser et al. ASCLEPIOS)



Figur 6. Kaplan-Meier-plot for effektmålet vedvarende sygdomsforværring (Hauser et al. OPERA)

Værdien af ofatumumab sammenlignet med ocrelizumab **kan ikke kategoriseres** efter Medicinrådets metoder.

Fagudvalget vurderer dog på baggrund af den kvalitative sammenligning, at ofatumumab og ocrelizumab sandsynligvis har omtrent samme effekt på effektmålet vedvarende sygdomsforværring. Det understøttes af, at virkningsmekanismen er identisk for de to lægemidler, og at effektforskellene i ASCLEPIOS og OPERA ligger på omtrent samme niveau.

Bivirkninger

Som beskrevet i protokollen er effektmålet bivirkninger et kritisk effektmål, da det belyser, hvor godt patienterne tolererer ofatumumab sammenlignet med komparator, og fordi patienterne kan være præget af mange alvorlige symptomer på deres sygdom. Fagudvalget ønskede både en kvantitativ opgørelse opgjort som antal patienter, der oplevede en eller flere alvorlige bivirkninger, og en kvalitativ gennemgang af ofatumumabs bivirkningsprofil.

Alvorlige bivirkninger

I ASCLEPIOS-studierne oplevede 9,1 % af patienterne en alvorlig uønsket hændelse ved behandling med ofatumumab, mens det samme tal i OPERA-studierne var 6,9 % ved behandling med ocrelizumab. Numerisk er der flere alvorlige uønskede hændelser i ASCLEPIOS-studierne, men patientpopulationernes forskelligartethed vanskeliggør en formel sammenligning.

Af EMAs EPAR fremgår det, at de hyppigst rapporterede alvorlige uønskede hændelser ved behandling med ocrelizumab var infektioner (1,3 %), forstyrrelser i nervesystemet (1,0 %) samt skader, forgiftning og komplikationer (0,7 %). 3,5 % afbrød behandling med ocrelizumab i studiet på grund af en alvorlig uønsket hændelse.

Numerisk er der relativt flere alvorlige uønskede hændelser i ASCLEPIOS-studierne, men patientpopulationernes forskelligartethed betyder, at den foreløbige værdi ikke kan kategoriseres efter Medicinrådets metoder. I tråd med at virkningsmekanismen er identisk, er der også et overlap i typen af de mest hyppige uønskede hændelser, hvor alvorlige infektioner er de hyppigste i begge studier.

Gennemgang af bivirkningsprofil

Tabel 9. Oversigt over bivirkninger i OPERA I & II

Variabel	OPERA I		OPERA II	
	Ocrelizumab (N=408)	Interferon Beta-1a (N=409)	Ocrelizumab (N=417)	Interferon Beta-1a (N=417)
Uønskede hændelser	327 (80,1)	331 (80,9)	360 (86,3)	357 (85,6)
Uønskede hændelser, der fører til behandlingsophør	13 (3,2)	26 (6,4)	16 (3,8)	25 (6,0)
Minimum én infusionsrelateret reaktion	126 (30,9)	30 (7,3)	157 (37,6)	50 (12,0)
Infektion	232 (56,9)	222 (54,3)	251 (60,2)	219 (52,5)
System organ class-infektion	231 (56,6)	216 (52,8)	251 (60,2)	217 (52,0)
Herpes infektion				
Herpes zoster	9 (2,2)	4 (1,0)	8 (1,9)	4 (1,0)
Oral herpes	9 (2,2)	8 (2,0)	15 (3,6)	9 (2,2)
Neoplasi	3 (0,7)	1 (0,2)	1 (0,2)	1 (0,2)
Død*	0	1 (0,2)	1 (0,2)	1 (0,2)
Alvorlige uønskede hændelser	28 (6,9)	32 (7,8)	29 (7,0)	40 (9,6)
Alvorlige infektioner	5 (1,2)	12 (2,9)	6 (1,4)	12 (2,9)

*Dødsfald, der opstod under studierne, skyldtes selvmord (én i ocrelizumab-gruppen i OPERA II-studiet og én i interferon beta-1a-gruppen i OPERA I-undersøgelsen) og mekanisk ileus (tarmobstruktion) (én i interferon beta-1a-gruppen i OPERA II-undersøgelse).

I lighed med ofatumumab vurderes de mest centrale sikkerhedsrisici ved behandling med ocrelizumab ifølge EMAs EPAR at være risikoen for infusionsrelaterede reaktioner og en øget infektionsrisiko.

Infusionsrelaterede reaktioner
Symptomer på infusionsrelaterede reaktioner i forbindelse med behandling med ocrelizumab omfatter bl.a. kløende hud, udslæt, nældefeber, rødme af huden, irritation eller smerter i halsen, åndenød, ødem i svælget eller strubehovedet, rødme, lavt blodtryk, feber, træthed, hovedpine, svimmelhed, kvalme, hjertebanken og anafylaksi. Der var ingen dødelige infusionsrelaterede reaktioner i de kontrollerede kliniske studier.

Infektioner
Infektionsincidensen ved behandling med ocrelizumab er sammenlignelig med IFNb, men patienter med alvorlige infektioner havde værre forløb end i komparatorarmen. Samtidig havde patienter med lymfocyttal under laveste normale grænse (LLN) større risiko for alvorlige infektioner, hvis de blev behandlet med ocrelizumab versus komparator.

I EMAs EPAR vurderes det, at klinisk relevante uønskede hændelser såsom injektionsrelaterede reaktioner, øvre luftvejsinfektioner, urinvejsinfektioner, herpes – eller varicella-zoster virusinfektioner – var hyppigere i ofatumumab-armen end i komparatorarmen i sikkerhedsdatasættet [11].

Langtidsbivirkninger
Et øget antal maligniteter (herunder brystkræft) er blevet observeret i kliniske studier hos patienter behandlet med ocrelizumab, sammenlignet med kontrolgrupperne. Forekomsten lå dog inden for, hvad der kan forventes for en MS-population. En individuel afvejning af fordele og ulemper skal overvejes hos patienter med kendte risikofaktorer for maligniteter og hos patienter, der aktivt monitoreres for recidiv af malignitet. Patienter med kendt aktiv malignitet må ikke behandles med ocrelizumab [13].

Der er ingen langtidssikkerhedsdata (> 5 år) for ofatumumab. Der pågår dog et *open label*-opfølgningsstudie, hvor patienter fra ASCLEPIOS kan fortsætte. Derfor mangler der viden om bivirkninger ved langtidsbehandling med ofatumumab.

Værdien af ofatumumab sammenlignet med ocrelizumab på effektmålet bivirkninger **kan ikke kategoriseres** efter Medicinrådets metoder. Fagudvalget vurderer dog, at sikkerheden overordnet er sammenlignelig, i og med at virkningsmekanismen er identisk for de to lægemidler. Der er dog forskel i dosering og administration samt i antistoffernes bindingssteder og derved depleteringsmekanisme. Disse forhold resulterer også i en forskel i, hvor lang tid det tager at gendanne B-celler efter afbrudt behandling med henholdsvis ofatumumab og ocrelizumab.

Årlig attakrate
Som beskrevet i protokollen er effektmålet årlig attakrate vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi attakker kan medføre varige funktionstab hos patienter med RRMS. Effektmålet dækker over antal attakker pr. år, hvorved en positiv ændring er et negativt resultat for patienterne.

Den årlige attakrate i ofatumumab-armen i ASCLEPIOS var henholdsvis 0,11 og 0,10 versus 0,16 i ocrelizumab-armen i OPERA.

Mht. den absolutte effektforskel reducerede ofatumumab i ASCLEPIOS den årlige attakrate med **0,128** vs. teriflunomid (95 % CI -0,163; -0,093), og ocrelizumab reducerede i OPERA den årlige attakrate med **0,136** vs. interferon beta-1a (95 % CI -0,188; -0,083).

Værdien af ofatumumab sammenlignet med ocrelizumab på effektmålet årlig attakrate **kan ikke kategoriseres** efter Medicinrådets metoder. Fagudvalget vurderer dog på baggrund af den kvalitative sammenligning, at ofatumumab og ocrelizumab sandsynligvis har omtrent samme effekt på årlig attakrate. Det understøttes af, at virkningsmekanismen er identisk for de to lægemidler, og at effektforskellene i ASCLEPIOS og OPERA ligger på omtrent samme niveau.

Kognitiv funktion
Som beskrevet i protokollen er effektmålet kognitiv funktion vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes kognitive funktion har stor betydning for patienternes trivsel og funktionsniveau.

Der er ingen data på effektmålet kognitiv funktion for ocrelizumab, og en sammenligning er derfor ikke mulig.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes livskvalitet har stor betydning for lægemidlets umiddelbare værdi for patienterne.

Der er brugt to forskellige mål for livskvalitet i studierne – SF-36 i OPERA og EQ5D-5L i ASCLEPIOS – og derfor er tallene ikke sammenlignelige.

[redacted]

For ocrelizumab var ændringerne fra baseline på 0,04 (95 % CI: -0,86; 0,93) i OPERA I og 0,33 (95 % CI: 0,55; 1,20) i OPERA II på SF-36.

Værdien af ofatumumab sammenlignet med ocrelizumab på effektmålet livskvalitet **kan ikke kategoriseres** efter Medicinrådets metoder. Fagudvalget vurderer, at det er sandsynligt, at ofatumumab og ocrelizumab har nogenlunde samme værdi vedr. livskvalitet, idet lægemidlerne har identisk virkningsmekanisme, og fordi der i studierne stort set ikke ses nogen ændring i patienternes livskvalitet.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af ofatumumab sammenlignet med ocrelizumab til patienter med attakvis MS **ikke kan kategoriseres**. Fagudvalget vurderer på baggrund af de tilgængelige studiedata, at det tyder på, at ofatumumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end ocrelizumab. Behandlingerne har samme virkningsmekanisme, og effektforskellene i de kliniske studier er på nogenlunde

samme niveau sammenlignet med deres respektive komparatorer (teriflunomid og interferon beta-1a), som fagudvalget anser for at have nogenlunde ligeværdig effekt [9].

Hvad angår sikkerheden af lægemidlerne, vurderer fagudvalget, at der er større usikkerhed angående langtidseffekt og bivirkninger for ofatumumab end for ocrelizumab, men fagudvalget vurderer det usandsynligt, at sikkerheden for ofatumumab er dårligere end for ocrelizumab.

6. Andre overvejelser

Da kvinder i den fødedygtige alder udgør en væsentlig del af patienter med MS, bør ønsker om graviditet være et opmærksomhedspunkt, når MS-behandling planlægges. Ofatumumab er et IgG-antistof og derfor i stand til at krydse placenta over i fosterets blodbane. B-celle-depleterende antistofbehandling er derfor kontraindiceret ved graviditet pga. mulig risiko for foster og nyfødt. Det anbefales, at kvinder anvender effektiv antikonception under B-celle-depleterende behandling og i minimum 6 måneder efter sidste behandling [14].

Medicinrådet har efterspurgt informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Ansøger beskriver, at skift fra ofatumumab kan være relevant ved manglende tolerabilitet eller graviditetsønske, og at alle andre typer sygdomsmodificerende behandling (DMT) i praksis bør kunne anvendes, med det forhold in mente, at effekten forventes at være mindre, hvis man skifter fra ofatumumab til moderat-effektiv DMT, hvilket svarer til førstelinjebehandling i dansk klinisk praksis.

Derudover bør patientens B-celleniveau være gendannet til tidligere normal, inden ny behandling startes. I og med at erfaringen med behandling med ofatumumab er begrænset, bør der ved behandlingsskift være ekstra opmærksomhed på uønskede hændelser.

7. Relation til behandlingsvejledning

Medicinrådet er i gang med at udarbejde en ny behandlingsvejledning og senere lægemiddelrekommandation til attakvis MS, og ofatumumab vil blive indplaceret i samme forbindelse.

8. Referencer

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Kristian Storr Overlæge, speciallæge i neurologi	Lægevidenskabelige Selskaber og udpeget af Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Regionen ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere et medlem	Region Midtjylland
Thor Petersen Overlæge	Region Syddanmark
Said Nasim Ashna Overlæge	Region Sjælland
Jeppe Romme Christensen Afdelingslæge	Region Hovedstaden
Hilde Omestad Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Freja Karuna Hemmingsen Sørup* 1. reservelæge	Dansk Selskab for Klinisk Farmakologi
Kan ikke opfylde Medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning Patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Malene Krüger Patient/patientrepræsentant	Danske Patienter
Matthias Kant Overlæge	Inviteret af formanden

*Har ikke deltaget i vurderingen af ofatumumab til behandling af attakvis multipel sklerose.

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	29. november 2021	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 10. Vurdering af risiko for bias, Hauser SL et al., 2020, ASCLEPIOS I (NCT02792218), ASCLEPIOS II (NCT02792231)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Brug af *interactive response technology* med valideret automatisk system til at randomisere patienter til behandling. Behandling blindet. Ingen tegn på signifikante forskelle i baseline karakteristika.
Effekt af tildeling til intervention	**Lav**	Det formodes, at patienter og personale i studiet ikke har kunnet udlede, om de modtog henholdsvis ofatumumab s.c. én gang om måneden eller teriflunomid p.o. én gang om dagen pga. det placebokontrollerede design. Derudover er der ingen indikationer på afvigelser i studieprotokollen.
Manglende data for effektmål	**Lav**	Op til ~17 % af patienterne i en behandlingsarm forlod studiet. Følsomhedsanalyser på ARR, CDW3/6 (table S3 & S4 i appendix) indikerer dog ikke, at det ville ændre hovedkonklusionen i studiet.
Risiko for bias ved indsamlingen af data	**Lav**	Vurderingen af endemål var blindet, og der er ingen indikationer på risiko for bias ved indsamling af data.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der er ingen indikationer på risiko for bias ved rapporterede resultater.
Overordnet risiko for bias	**Lav**	Ingen indikationer på bias.

Tabel 11. Vurdering af risiko for bias *Hauser SL et al., 2017*, OPERA I (NCT01247324), OPERA II (NCT01412333)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Brug af *independent interactive Web-response system* til at randomisere patienter til behandling. Behandling blindet. Ingen tegn på signifikante forskelle i baseline karakteristika.
Effekt af tildeling til intervention	**Lav**	Der er en risiko for, at behandlingserfarne MS-patienter har kunnet udlede, om de har modtaget IFN eller ocrelizumab pga. bivirkningsprofilen for IFN-behandling. I OPERA I forlod 10 % vs. 17 %, I OPERA II 14 % vs. 23 % for helholdsvis intervention og komparator. Det kan ikke udelukkes, at kendskab til tildelt behandlingsarm kan have haft betydning for frafald eller adfærd i studiet.
Manglende data for effektmål	**Lav**	Op til ~23 % af patienterne i en behandlingsarm forlod studiet.
Risiko for bias ved indsamlingen af data	**Lav**	Vurderingen af endemål var blindet, og der er ingen indikationer på risiko for bias ved indsamling af data.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der er ingen indikationer på risiko for bias ved rapporterede resultater.
Overordnet risiko for bias	**Lav**	

Bilag 2: GRADE

Klinisk spørgsmål 1 – ofatumumab sammenlignet med teriflunomid til behandling af patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet

Tabel 12. GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ofatumumab	Ocrelizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
2	RCT	Lav	Ingen	Alvorlig[a]	Ingen	Ingen	946	936	0,655 (95 % CI: 0,500; 0,858)	-4,90 %-point (95 % CI: -7,20; -1,98)	⨁⨁⨁◯ MODERAT	Kritisk
Bivirkninger												
2	RCT	Lav	Ingen	Meget alvorlig[b]	Alvorlig[c]	Ingen	946	936	1,151 (95 % CI: 0,855; 1,550)	1,1 %-point (95 % CI: -1,4; 3,6)	⨁◯◯◯ MEGET LAV	Kritisk
Årlig attakrate												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ofatumumab	Ocrelizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
2	RCT	Lav	Ingen	Alvorlig[a]	Alvorlig[c]	Ingen	946	936	ASCLEPIOS I: RR 0,49 (95 % CI: 0,37; 0,65) ASCLEPIOS II: RR 0,42 (95 % CI: 0,31; 0,56)	-0,128 årlig attakrate (95 % CI: -0,163; -0,093)	⨁⨁◯◯ LAV	Vigtig
Kognitiv funktion												
2	RCT	Lav	Ingen	Alvorlig[a]	Ingen	Ingen	946	936	[redacted]	[redacted]	⨁⨁⨁◯ MODERAT	Vigtig
livskvalitet												
2	RCT	Lav	Ingen	Alvorlig[a]	Ingen	Ingen	946	936	NA	[redacted]	⨁⨁⨁◯ MODERAT	Vigtig
Kvalitet af den samlede evidens	MEGET LAV[d]											

[a] Der er nedgraderet ét niveau, da der var indirekthed ift. den danske population.
[b] Der er nedgraderet to niveauer, da der var indirekthed ift. den danske population og derudover indleveret data på uønskede hændelser i stedet for bivirkninger.
[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder én beslutningsgrænse.
[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Medicinrådet

Application for the assessment of ofatumumab for treatment of adult patients with relapsing forms of multiple sclerosis (RMS)

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1. Basic information

Contact information	
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NHTA, Tømmergravsgade 6, 2450 Copenhagen SV, prepared the health economic part of the application.

Larix A/S, Lyskær 8b, DK-2730 Herlev, provided statistical and medical writing support.

Overview of the pharmaceutical	
Proprietary name	Kesimpta®
Generic name	Ofatumumab
Marketing authorization holder in Denmark	Novartis Ireland Limited Vista Building Elm Park, Merrion Road Ballsbridge Dublin 4 Ireland
ATC-code	L04AA52
Pharmacotherapeutic group	Selective immunosuppressant
Active substance	Ofatumumab
Pharmaceutical form	Solution for injection (injection) in pre-filled pen (Sensoready Pen). This medicinal product is intended for patient self-administration by subcutaneous injection after an initial instruction by a health care professional (week 0).
Mechanism of action	Ofatumumab is a fully human anti-CD20 monoclonal immunoglobulin G1 (IgG1) antibody produced by recombinant DNA technology. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells. The binding of ofatumumab to CD20 induces lysis of CD20+ B cells primarily through complement-dependent cytotoxicity (CDC) and, to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.
Dosage regimen	The recommended dose is 20 mg ofatumumab administered by subcutaneous injection with: - initial dosing at weeks 0, 1 and 2, followed by - subsequent monthly dosing, starting at week 4
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. It is specified in the European public assessment report (EPAR) for Kesimpta that the indication applies both to newly diagnosed patients and patients who are treated with another disease-modifying therapy and are switching therapy due to lack of efficacy or for safety or tolerability issues [1].

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Overview of the pharmaceutical	
Other approved therapeutic indications	None. Ofatumumab was previously approved for treatment of chronic lymphatic leukaemia (CLL) under the proprietary name Arzerra®. For this indication, ofatumumab was administered intravenously (i.v.), more frequently and at considerably higher doses (300-2000 mg) compared to the doses used for multiple sclerosis (MS). Arzerra® was de-registered in Europe in February 2019 due to the evolving CLL treatment landscape.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Premedication prior to injection is not required
Packaging – types, sizes/number of units, and concentrations	One pre-filled pen containing 20 mg ofatumumab in 0.4 ml solution (50 mg/ml)
Orphan drug designation	No
Other information	On April 22, 2021, the National Institute for Health and Care Excellence (NICE), UK, recommended ofatumumab as an option for treating relapsing-remitting multiple sclerosis (RRMS) in adults with active disease defined by clinical or imaging features [2].

Confidential data is marked in yellow.

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2. Abbreviations

6mCCD	6-month confirmed cognitive impairment
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine transaminase
ARR	Annualised relapse rate
BMI	Body mass index
CDC	Complement-dependent cytotoxicity
CDP	Confirmed disability progression
CDP-3	Confirmed disability progression after 3 months
CDW	Confirmed disability worsening (the same as confirmed disability progression)
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CLL	Chronic lymphatic leukaemia
CYP	Cytochrome P450
DHO-DH	Dihydroorotate dehydrogenase
DILI	Drug-induced liver injury
DMT	Disease-modifying therapy
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSUR	Development safety update report
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol Group 5-dimension health-related quality of life instrument
EQ-5D-5L	EuroQol Group 5-dimension health-related quality of life instrument 5-level
Fs	Functional score
Gd+	Gadolinium-enhancing
IgA	Immunoglobulin A
IgG1	Immunoglobulin G1
IgM	Immunoglobulin M
IIR	Infusion-related reaction
ITT	intention to treat
i.v.	Intravenously
JC	John Cunningham
LLN	Lower limit of normal
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NCT	National clinical trial
NICE	National institute for health and care excellence
NfL	Neurofilament light chain
OAT3	Organic anion transporter 3
OATP1B1/B3	Organic anion transporting polypeptide B1 and B3
OLE	Open-label extension
PICO	Population, Interventions, Comparisons, Outcomes
PML	Progressive multifocal leukoencephalopathy

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PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBC	Red blood cells
RCT	Randomised clinical trial
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
s.c.	Subcutaneously
SDMT	Symbol digit modalities test
SF-36	36-item short form health survey
SJS	Steven Johnson syndrome
SmPC	Summary of product characteristics (produktresumé)
SPMS	Secondary progressive multiple sclerosis
TEN	Toxic epidermal necrosis
ULN	Upper limits of normal
VAS	Visual analogue scale
vs.	Versus
WBC	White blood cell

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3. Summary

Ofatumumab is a fully human anti-CD20 monoclonal immunoglobulin G1 (IgG1) antibody, indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features [3]. This indication includes newly diagnosed patients and patients who are treated with another disease-modifying therapy (DMT), but where switching is needed either due to lack of efficacy or for safety or tolerability reasons. Ofatumumab is to be administered subcutaneously at a dose of 20 mg, with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing starting at week 4. Ofatumumab can be self-administered after an initial instruction by a health care professional (week 0).

Ofatumumab is compared with teriflunomide in patients with average disease activity ('first-line' therapy) and with ocrelizumab in patients with high disease activity ('second-line'). The comparison of efficacy vs. teriflunomide is a direct comparison based on the ASCLEPIOS I and II studies [4]. The comparison of efficacy vs. ocrelizumab is a narrative comparison based on the pivotal phase 3 studies ASCLEPIOS I and II for ofatumumab and OPERA I and II [4] for ocrelizumab. Comparison of safety profiles are, in addition to the clinical study results, based on the Summary of Product Characteristics (SmPCs) of the three products.

Ofatumumab was statistically significantly more effective than teriflunomide regarding confirmed disability progression (CDP) after three months (CDP-3, relative difference 0.655, 95% confidence interval [CI] 0.500;0.858, p=0.0021), annualised relapse rate (ARR, absolute difference -0.128, 95% CI -0.163;-0.093, p<0.0001) and quality of life measured by EQ-5D-5L utility score (absolute difference 0.023, 95% CI 0.004;0.041, p=0.018). The difference between treatments for cognition, measured by the Symbol Digit Modalities Test (SDMT), was not significant. The incidence of adverse events (AEs) and serious adverse events (SAEs) were similar for ofatumumab and teriflunomide, including the proportion of patients with infections. No opportunistic infections were reported. Local and systemic injection-related reactions were reported, respectively, for 10.9% and 20.6% of the ofatumumab treated patients and were mostly (99.8%) mild to moderate in severity, and systemic related injection reactions were primarily reported after the first injection. For teriflunomide, the SmPC states that cases of life-threatening liver injury as well as fatal cases or severe skin reactions have been reported post-marketing. Concomitant medication must be carefully considered due to several drug-drug interactions with teriflunomide, and close monitoring of liver enzymes, blood pressure and white blood cell count is also required.

The efficacy of ofatumumab and ocrelizumab seems to be in the same range, with CDP-3 experienced by 10.9% and 9.1% of patients, respectively (risk reduction vs. teriflunomide of 34.5%, and risk reduction vs. interferon beta-1a of 39.7, respectively). In terms of ARR, ofatumumab decreased ARR by 0.128 vs. teriflunomide (95% CI -0.163;-0.093, p<0.0001) and ocrelizumab decreased ARR by 0.136 vs. interferon beta-1a (95% CI -0.166;-0.083, p<0.0001). Comparison of the effects on quality of life and cognition was not possible, as different scales were used in the ASCLEPIOS and OPERA studies, and SDMT data were not published. Ofatumumab may have a more favourable safety profile vs. ocrelizumab, e.g. pre-medication is required in relation to i.v. infusion of ocrelizumab, and neutropenia and IgG depletion is listed for ocrelizumab only and monitoring due to potential changes of IgG and IgM is required. No opportunistic infections occurred during the clinical studies. A few post-marketing cases of progressive multifocal leukoencephalopathy (PML) have been reported for ocrelizumab, the majority in patients previously treated with other DMTs. PML is a listed adverse drug reaction for natalizumab, fingolimod, and dimethyl fumarate [5-7]. An open-label long-term follow-up study of ofatumumab in RMS, ALITHIOS [8], is ongoing, and a 3.5 year safety update is planned to be presented at the European Academy of Neurology congress in June 2021. [redacted]

In relation to pregnancy, ofatumumab offers a better safety profile, both versus teriflunomide and ocrelizumab. The time to B-cell repletion is faster for ofatumumab vs. ocrelizumab, and therefore, treatment with ofatumumab and ocrelizumab should be discontinued 6 and 12 months prior to stopping contraception, respectively [3, 9].

Ofatumumab has the potential to reduce the burden associated with the increasing use of infusion therapies at hospitals, which is even more critical under the current capacity constraints imposed by the COVID-19 pandemic. In contrast to ocrelizumab, which is administered in hospitals via infusions lasting several hours, ofatumumab will be provided in pre-filled auto-injector pens for subcutaneous injection, intended for monthly self-administration at home by patients or their carers after an initial instruction by a health care professional (week 0). It is considered that the

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introduction of a subcutaneous high-efficacy B cell therapy will significantly reduce the burden and capacity issues associated with the i.v. administration of ocrelizumab and other high-efficacy DMTs.

The ASCLEPIOS study results demonstrated that ofatumumab is more efficacious than teriflunomide and is generally well tolerated, with an acceptable and manageable AE profile and minimal monitoring required. As a monthly self-administered treatment, ofatumumab will be the first B cell therapy accessible for all patients with RMS, providing a high-efficacy and well-tolerated treatment option. Ofatumumab therefore has the potential to shift the treatment paradigm in the RMS population towards early use of high-efficacy treatment. The latter has been associated with improvements in clinical outcome, also shown in a Danish patient population [10].

Based on a narrative comparison across studies, ofatumumab and ocrelizumab seem to be equally efficacious, and ofatumumab may have a better safety profile than ocrelizumab. It is considered that the introduction of a subcutaneous high-efficacy B cell therapy will significantly reduce the burden and capacity issues associated with the i.v. administration of ocrelizumab and other high-efficacy DMTs.

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4. Literature search

4.1 Databases and search strategy

For clinical question 1, no literature search was conducted, as there are two studies where ofatumumab is compared directly to teriflunomide. The data provided in the publication *Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020;383(6):546-57* [4] is considered as sufficient for answering the clinical question according to the protocol provided by the Danish Medicines Council. In addition, the European public assessment reports (EPARs) from the European Medicines Agency (EMA) for the two products have been consulted [1, 11].

For clinical question 2, a systematic literature review was conducted to identify relevant publications to assess the clinical added value of ofatumumab for the treatment of RMS versus ocrelizumab.

The systematic literature review included the search string as defined in the protocol provided by the Danish Medicines Council. The results from the systematic search performed on April 28, 2021 in Medline and in the Cochrane Central Register of Controlled Trials (CENTRAL) are presented in Table 1 and Table 2, respectively.

Table 1 Search string and results of the systematic search in Medline (via PubMed)

History and Search Details — Download — Delete

Search	Actions	Details	Query	Results	Time
#12	•••	>	Search: **#10 NOT #11**	28	07:37:58
#11	•••	>	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR case report[ti]**	6,580,773	07:37:39
#10	•••	>	Search: **#8 AND #9**	66	07:37:15
#9	•••	>	Search: **(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans[mh])**	1,304,091	07:36:52
#8	•••	>	Search: **#4 AND #7**	248	07:36:34
#7	•••	>	Search: **#5 OR #6**	1,048	07:36:19
#6	•••	>	Search: **ocrelizumab[nm] OR ocrelizumab[tiab] OR Ocrevus*[tiab]**	482	07:36:02
#5	•••	>	Search: **ofatumumab[nm] OR ofatumumab[tiab] OR Kesimpta*[tiab] OR Arzerra*[tiab] OR Humax*[tiab]**	647	07:35:47
#4	•••	>	Search: **#1 OR #2 OR #3**	31,626	07:35:12
#3	•••	>	Search: **relaps*[tiab] AND (multiple sclerosis[tiab] OR MS[tiab])**	16,065	07:34:54
#2	•••	>	Search: **RMS[tiab] OR RRMS[tiab] OR RR-MS[tiab]**	17,817	07:34:20
#1	•••	>	Search: **Multiple Sclerosis, Relapsing-Remitting[mh]**	6,563	07:33:29

Showing 1 to 12 of 12 entries

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Table 2 Search string and results of the systematic search in CENTRAL (via Cochrane library)

Search | Search manager | Medical terms (MeSH) | PICO search BETA

Save this search | View saved searches | ? Search help

View fewer lines | Print

#1	[mh "Multiple Sclerosis, Relapsing-Remitting"]	Limits	898
#2	multiple sclerosis:kw and embase:an and relaps*:ti,ab,kw	Limits	2384
#3	(RMS or RRMS OR "RR MS"):ti,ab	Limits	2763
#4	(relaps* and (multiple next sclerosis or MS)):ti,ab	Limits	4656
#5	#1 OR #2 OR #3 OR #4	Limits	5813
#6	(ofatumumab or Kesimpta* or Arzerra* or Humax*):ti,ab,kw	Limits	318
#7	(ocrelizumab or Ocrevus*):ti,ab,kw	Limits	243
#8	#6 or #7	Limits	558
#9	#5 and #8	Limits	186
#10	(clinicaltrials.gov or trialsearch):so	Limits	362707
#11	NCT*:au	Limits	205912
#12	("conference abstract" or review):ti,pt	Limits	195421
#13	(abstract or conference or meeting or proceeding*):so	Limits	44833
#14	#10 or #11 or #12 or #13	Limits	587855
#15	#9 not #14	Limits	28
#16	Type a search term or use the S or MeSH buttons to compose	S MeSH Limits	N/A

Clear all | Highlight orphan lines

Of the 28 records identified in CENTRAL, 26 were in 'Trials', 1 was in 'Cochrane reviews' and 1 was in 'Cochrane protocols'.

The eligibility criteria used for the systematic literature review are defined in terms of the Population, Interventions, Comparisons, Outcomes (PICOs) and study design framework as well as language and time frame (see Table 12 in Appendix 7.1).

A total of 54 records were identified through CENTRAL and MEDLINE. With duplicates removed (n = 16), 40 records were left to be screened. Two reviewers, working independently, reviewed the identified records for inclusion by title or abstract according to the PICO selection criteria, resulting in 27 excluded records. The 9 full-text publications that passed the first screening underwent a more rigorous screening to assess any data of interest according to PICO. Of these, two publications corresponding to four clinical studies were found relevant, further described in section 4.3.

The process of study identification and selection is summarised in Figure 1 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

All records excluded after full-text review are presented with reason for exclusion in Table 13 in Appendix 7.1.

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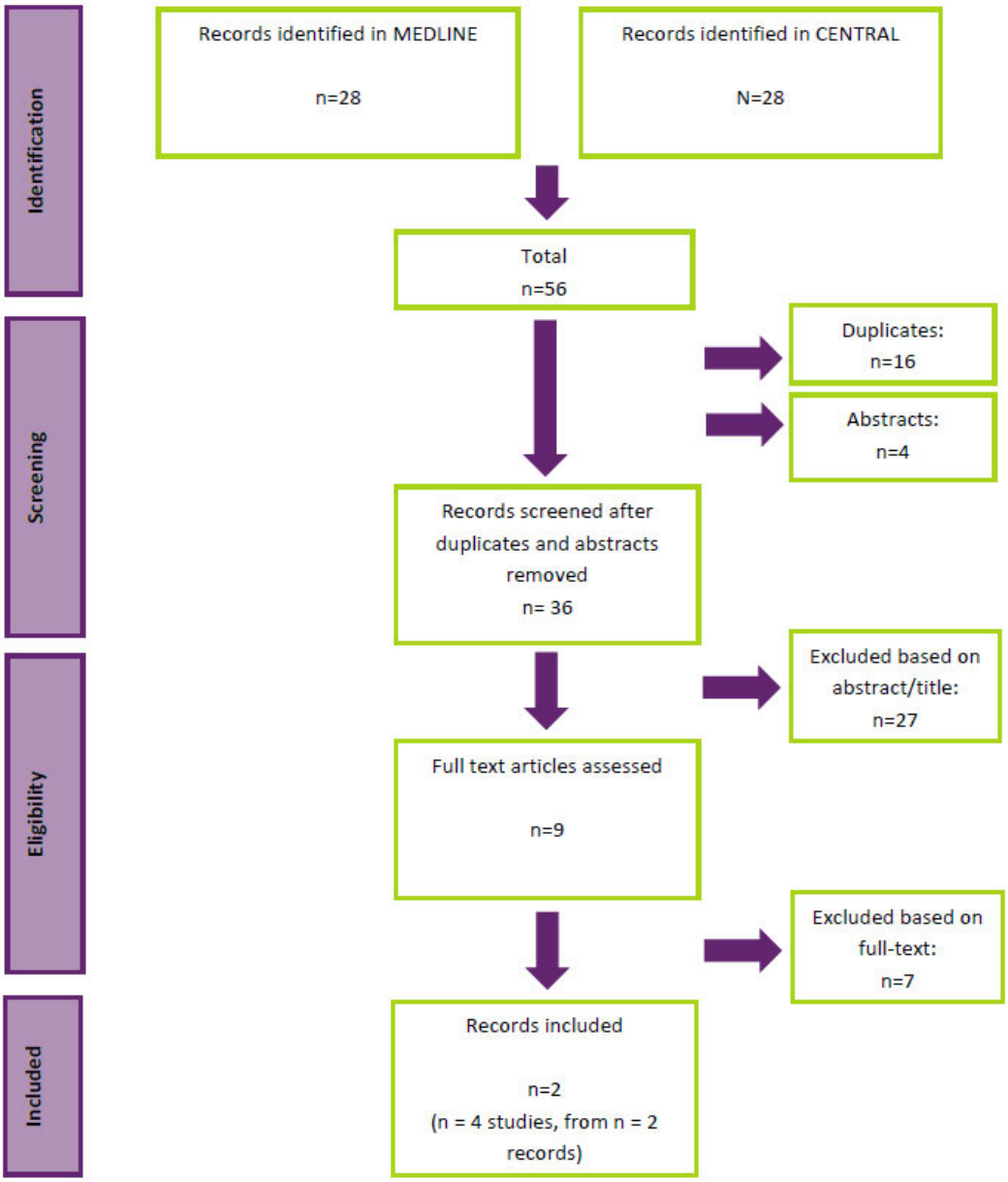
Figure 1 PRISMA flow diagram



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CENTRAL = Cochrane Central Register of Controlled Trials

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4.2 Relevant studies

Table 3 Relevant studies included in the assessment

Reference	Study name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Ofatumumab versus teriflunomide in multiple sclerosis. Hauser SL et al. N Engl J Med. 2020 [4]	ASCLEPIOS I	NCT02792218	Start: Sep 20, 2016 Primary completion: Jul 05, 2019 Completion: Jul 20, 2020	1 and 2
	ASCLEPIOS II	NCT02792231	Start: Aug 26, 2016 Primary completion: Jul 10, 2019 Completion: Oct 22, 2020	1 and 2
Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. Hauser SL et al. N Engl J Med. 2017 [12]	OPERA I	NCT01247324	Start: Aug 31, 2011 Primary completion: Apr 2, 2015 Estimated completion: Dec 28, 2023	2
	OPERA II	NCT01412333	Start: Sep 20, 2011 Primary completion: May 12, 2015 Estimated completion: Dec 28, 2023	2

4.3 Main characteristics of included studies

A total of four studies are included in the assessment of the clinical questions defined in the protocol: ASCLEPIOS I and II and OPERA I and II. All four studies are randomised, controlled phase III studies. The main characteristics of the included studies are presented in Table 14 to Table 17 in Appendix 7.2. Relevant differences between the ASCLEPIOS studies and the OPERA studies are discussed in the section 5.2.1 (study and baseline characteristics) and section 5.2.2 (relevant outcomes). Results for all included studies are included in the tables in Appendix 7.3.

4.3.1 Included studies in relation to the PICO framework

Populations included in the analyses

The population for clinical question 1 is 'patients with RMS and average disease activity', and the population for clinical question 2 is 'patients with RMS and high disease activity'. There is currently no clear definition of 'average disease activity' and 'high disease activity', neither in the treatment guidelines from the Medicines Council or the international guidelines [13, 14] nor in the clinical setting according to Danish clinical experts in multiple sclerosis (MS). In the included clinical studies, a group of patients with average vs. high disease activity has not been specified, neither by eligibility criteria nor by pre-defined subgroups. For this reason and because a split of data into subgroups (which may not fully cover the population in question) will dilute the strength of the data, results from the full study populations are included in the comparative analysis. This approach was also used in the applications to the Medicines Council for ocrelizumab and ozanimod in RMS [15, 16] and has been agreed with the Medicines Council during the dialogue meeting.

Dose of ofatumumab in the clinical and economic part of the application

The dose for ofatumumab used in the clinical part of the application is 20 mg administered subcutaneously every 4 weeks (initial doses on day 1, 7 and 14), which was also used in the clinical studies [4]. It differs marginally from the recommended dose in the SmPC [3], which is monthly dosing after the initial doses. As agreed during the dialogue

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meeting, the calculations in the economic part of the application will be based on the dosing in the SmPC, as this will be the regimen used in clinical practice.

4.4 Data on file

Data included in this application on SDMT and EQ-5D from the ASCLEPIOS studies has not been published. The data is included to address the clinical questions. Data on SDMT and EQ-5D is currently under consideration to be submitted to a peer reviewed journal within the next year. We therefore consider these data confidential.

Information on IgG levels from the open-label long-term follow-up study, ALITHIOS [8] (conducted in accordance with the CONSORT rules, to the extent that it applies to open-label studies), are included, as it is considered to be relevant information on long-term (up to 3.5 years) safety of ofatumumab in patients with MS. The data will be presented at the EAN congress as an oral presentation (late braking news) on 23 June 2021 and is therefore confidential until then. Submission to a peer review journal is planned for July 2021.

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5. Clinical questions

5.1 Clinical question 1: What is the value of ofatumumab compared to teriflunomide for patients with RMS and average disease activity (first line treatment)?

5.1.1 Presentation of relevant studies

The comparison between ofatumumab and teriflunomide is based on two phase 3 randomised controlled trials (RCTs), namely, ASCLEPIOS I and ASCLEPIOS II, which were both identical in design [4]. The RCTs were double-blind, double-dummy, active comparator-controlled, parallel-group, multicentre adaptive and flexible duration design studies, where patients with relapsing forms of multiple sclerosis (RRMS or secondary progressive multiple sclerosis [SPMS]) with disease activity as defined by Lublin et al. 2014 [14] were randomised 1:1 to subcutaneous ofatumumab (20 mg every 4 weeks after 20 mg loading doses at days 1, 7 and 14) or oral teriflunomide (14 mg daily) for up to 30 months. The primary endpoint was the ARR. Secondary key endpoints included disability worsening confirmed at 3 months or 6 months, disability improvement confirmed at 6 months, the number of gadolinium-enhancing lesions per T1-weighted magnetic resonance imaging (MRI) scan, the annualised rate of new or enlarging lesions on T2-weighted MRI scan, serum neurofilament light chain levels at month 3, and brain volume loss. Overall, 946 patients were assigned to receive ofatumumab and 936 to receive teriflunomide. The median follow-up time was 1.6 years.

Baseline characteristics were well balanced across the treatment arms (see Table 14 and Table 15 in Appendix 7.2).

Further details on study design, eligibility criteria and endpoints and baseline characteristics are presented in Table 14 and Table 15 in Appendix 7.2)

5.1.2 Results per study

All efficacy results are presented for the intention to treat (IIT) populations. All safety results are presented for the safety populations.

Confirmed disability progression at 3 months (CDP-3)

In the ASCLEPIOS studies, the term 'confirmed disability worsening' (CDW) was used instead of 'confirmed disability progression' (CDP). The difference is semantic and based on the recommendation by the US National Multiple Sclerosis Society, which suggests using the term 'worsening' in RMS and 'progression' in progressive phases, where the worsening is independent of attacks [14]. For this application, the outcome is called 'CDP'.

In ASCLEPIOS I and II, the proportion of patients with CDP-3 was a key secondary endpoint. CDP-3 was defined as an increase from baseline Expanded Disability Status Scale (EDSS) score (on a scale from 0 to 10.0, with higher scores indicating worse disability) that was sustained for at least 3 months. For patients with a baseline EDSS score of 0, an increase in the EDSS score of at least 1.5 points was required; for patients with a baseline EDSS score of 1.0 to 5.0, the criterion was an increase of at least 1.0 point; and for patients with a baseline EDSS score of at least 5.5 points, the criterion was an increase of at least 0.5 points. Results shown below are based on Kaplan-Meier estimates at 24 months.

In the ASCLEPIOS I study, the proportion of patients with CDP-3 was 11.3% for ofatumumab and 15.4% for teriflunomide, resulting in an estimated absolute difference of -4.1% points and an estimated relative difference of 0.650 (95% CI 0.45;0.96), p=0.026.

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In the ASCLEPIOS II study, the proportion of patients with CDP-3 was 10.5% for ofatumumab and 14.6% for teriflunomide, resulting in an estimated absolute difference of -4.1% points and an estimated relative difference of 0.66 (95% CI 0.44;0.97), p=0.034.

In conclusion, in the ASCLEPIOS I and II trials, statistically significant risk reductions of 35.0% and 34.0%, respectively, for CDP-3 was achieved with ofatumumab when compared with teriflunomide.

Results are shown in Table 18 and Table 19, Appendix 7.3.

Serious adverse events and adverse events

AEs (treatment emergent AEs, regardless of relation to study drug) up to 100 days after the last administration of a study drug, SAEs up to the last visit by the last patient, AEs leading to treatment discontinuation, and deaths in the ASCLEPIOS I and II studies are summarized in Table 4 [4].

Table 4 Safety results of the ASCLEPIOS I and II studies

Variable	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Any adverse event	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)
Adverse event leading to treatment discontinuation	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)
Infection	229 (49.2)	238 (51.5)	259 (53.8)	255 (53.8)
Injection-related systemic reaction	75 (16.1)	76 (16.5)	116 (24.1)	64 (13.5)
Serious adverse event	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)
Serious infection	12 (2.6)	7 (1.5)	12 (2.5)	10 (2.1)
Serious injection-related reaction	2 (0.4)	0	0	0
Neoplasm	3 (0.6)	3 (0.6)	2 (0.4)	1 (0.2)
Death[1]	0	0	0	1 (0.2)

Numbers represent the number of patients (%), safety population.

1: The cause of death was aortic dissection.

AEs that occurred in at least 10% of the patients treated with ofatumumab were injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection and urinary tract infection.

AEs that occurred in at least 10% of those treated with teriflunomide were nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache and diarrhoea.

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A detailed comparison between the safety profiles of ofatumumab and teriflunomide is presented and discussed in section 5.1.3.

In conclusion, the ASCLEPIOS study results demonstrated a favourable safety profile of ofatumumab. Ofatumumab was generally well tolerated compared to teriflunomide.

Proportion of patients experiencing an SAE is also shown in Table 18 and Table 19, Appendix 7.3.

Annualised relapse rate (ARR)

The ARR was the primary outcome in the ASCLEPIOS studies.

- The ARR was defined as the number of confirmed relapses of MS per year, according to prespecified criteria.
- A relapse was defined as the appearance of a new neurological abnormality or worsening of a previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection. The assessment, management and reporting of MS relapses was made by the investigator.
- A confirmed MS relapse was defined as a relapse accompanied by a clinically relevant change in the EDSS score performed by the independent EDSS rater (i.e., an increase of at least 0.5 points on the EDSS score, or an increase of 1.0 point on two functional scores [FSs] or 2.0 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previously available rating – i.e., the last EDSS rating that did not occur during a relapse). Confirmation of MS relapse based on these definitions was done centrally.

In the ASCLEPIOS I study, the ARR was 0.11 (95% CI 0.09;0.14) for ofatumumab and 0.22 (95% CI 0.18;0.26) for teriflunomide, resulting in an estimated absolute difference of -0.11 (95% CI -0.16;-0.06), p<0.0001, and an estimated relative difference of 0.49 (95% CI 0.37;0.65), p<0.001.

In the ASCLEPIOS II study, the ARR was 0.10 (95% CI 0.08;0.13) for ofatumumab and 0.25 (95% CI 0.21;0.3) for teriflunomide, resulting in an estimated absolute difference of -0.15 (95% CI -0.2;-0.09), p<0.0001, and an estimated relative difference of 0.42 (95% CI 0.31;0.56), p<0.001.

In conclusion, in the ASCLEPIOS I and II studies, ofatumumab reduced the ARR by 51% and 58%, respectively, compared to teriflunomide, a difference that was both statisically significant and above the minimal clinically important difference of 1.0 [17].

The results are shown in Table 18 and Table 19, Appendix 7.3.

Cognitive function

Time to a 6-month confirmed cognitive impairment (6mCCD) defined as a 4-point deterioration measured by the SDMT was an exploratory endpoint in the ASCLEPIOS I and II studies.

The SDMT is a sensitive and specific test to assess processing speed, which is typically affected in cognitively impaired MS patients. Patients are to match symbols and numbers from a predefined key; the score is determined from the number of matching combinations that the patient has achieved over 90 seconds and can reach a maximum of 110 points. The test takes approximately 5 minutes to administer. Alternate versions of the SDMT are to be used in an alternating pattern to minimise learning effects. A 10% deterioration and a 4-point deterioration are considered equally clinically relevant [18, 19].

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Data on SDMT from the ASCLEPIOS studies has not been published. The following is based on 24-week results from the data on file.

[redacted]

[redacted]

In conclusion, none of the ASCLEPIOS studies showed a difference between ofatumumab and teriflunomide regarding effect on cognition measured by the SDMT. However, based on discussions with Danish clinical experts in MS, significant changes in cognitive impairment in an RMS population upon treatment with a DMT cannot be expected as early as over a 2-year period.

The results are shown in Table 18 and Table 19, Appendix 7.3.

Quality of life

EQ-5D-5L was assessed in the ASCLEPIOS I and II studies. The EQ-5D measures five domains (mobility, self-care, usual activity, pain/discomfort & anxiety/depression). There are 2 parts to this questionnaire. The first, 'health state classification' consists of five questions, with lower scores indicating better health. The second, 'visual analogue scale thermometer' consists of a visual analogue scale ranging from 0-100, where a higher score indicates better health. The EQ-5D utility scores were assessed according to guidelines established by health technology assessment authorities (e.g., UK NICE; EuroQol Group 1990) (data on file).

Data on EQ-5D from the ASCLEPIOS studies has not been published. The following is based on 96-week results from the data on file.

[redacted]

[redacted]

In conclusion, the changes from baseline in EQ-5D utility and VAS score in the ASCLEPIOS I and II studies were numerically higher for ofatumumab in both studies, and statistically significantly higher for ofatumumab in the ASCLEPIOS II study.

Results are shown in in Table 18 and Table 19, Appendix 7.3.

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5.1.3 Comparative analyses

The comparative analysis between ofatumumab and teriflunomide is based on the ASCLEPIOS I and ASCLEPIOS II studies. The statistical methods are described, and the forest plots for the meta-analyses are shown in Appendix 7.6.

Confirmed Disability Progression at 3 months (CDP-3)

The absolute difference in effect between ofatumumab and teriflunomide was -4.90 (95% CI -7.20 ; -1.98), and the relative difference in effect was 0.655 (95% CI 0.500;0.858), p=0.0021.

In conclusion, ofatumumab significantly reduced the risk of CDP-3 by 34.5% vs. teriflunomide.

The results are shown in Table 22, Appendix 7.4 and the forest plots are shown in Appendix 7.6.

Adverse reactions

Serious adverse events
In the ASCLEPIOS I and II studies, 9.1% of the patients in the ofatumumab treatment arms and 7.9% of the patients in the teriflunomide treatment arms experienced at least one SAE [1].

The absolute difference between treatments was 1.116% points (95% CI -1.394;3.625), and the relative difference between treatments was 1.151 (95% CI 0.855;1.550), p=0.355.

The difference between the treatments is lower than the minimal clinically important difference of 3% points as defined in the protocol [17].

In conclusion, there was no statistically significant difference between ofatumumab and teriflunomide in the proportion of patients experiencing an SAE.

The results are shown in Table 22, Appendix 7.4 and the forest plots are shown in Appendix 7.6.

General safety profile
The Medicines Council has asked for a review of the safety profiles of ofatumumab and teriflunomide based on both clinical data and the SmPCs. A comprehensive overview of safety information in the SmPCs is included in Appendix 7.5.

Unless otherwise stated, the information in this section is based on the approved SmPCs for teriflunomide and ofatumumab [3, 11].

Mode of action
Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of T-lymphocytes.

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Ofatumumab is a fully human anti-CD20 monoclonal IgG1 antibody. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells. The binding of ofatumumab to CD20 induces lysis of CD20+ B cells primarily through complement-dependent cytotoxicity (CDC) and, to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.

Contraindications
Teriflunomide is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients; patients with severe hepatic impairment or immunodeficiency states; patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia; patients with severe active infection until resolution; patients with severe renal impairment undergoing dialysis or having severe hypoproteinaemia, e.g. in nephrotic syndrome; and pregnant women or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter, as long as its plasma levels are above 0.02 mg/l (pregnancy must be excluded before the start of treatment) or beast-feeding women.

Ofatumumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients and in patients in a severely immunocompromised state or having severe active infection until resolution or known active malignancy.

Most common adverse events
For **teriflunomide**, the most commonly reported adverse reactions, as described in the SmPC, were headache, diarrhoea, increased alanine transaminase (ALT), nausea, and alopecia. In general, headache, diarrhoea, nausea and alopecia were mild to moderate, transient and infrequently led to treatment discontinuation. In addition, in the ASCLEPIOS studies, nasopharyngitis, injection-related reactions (with placebo), and upper respiratory tract infection were seen in at least 10% of those treated with teriflunomide [4].

For **ofatumumab**, the most commonly reported adverse reactions, as described in the SmPC, were upper respiratory tract infections, systemic injection-related reactions, injection-site reactions and urinary tract infections. In addition, in the ASCLEPIOS studies nasopharyngitis and headache were seen in at least 10% of those treated with ofatumumab [4].

Adverse reactions of special interest
Infections
In the ASCLEPIOS studies, the overall rate of infections and serious infections in patients treated with **ofatumumab** was similar to the rate in patients treated with **teriflunomide** (51.6% vs. 52.7% and 2.5% vs. 1.8%, respectively). Two patients (0.2%) discontinued, and 11 patients (1.2%) temporarily interrupted study treatment due to a serious infection.

Infections reported in more than 10 % in either of the treatment groups in the ASCLEPIOS studies are shown in Table 5.

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Table 5 Infections reported in 10% or more of patients in the ASCLEPIOS studies

	Ofatumumab	Teriflunomide
Nasopharyngitis	18.0%	16.7%
Upper respiratory tract infection	10.3%	12.8%
Urinary tract infection	10.3%	8.3%

Herpes-associated infection occurred in 4.9% and 4.2%, respectively, with ofatumumab and teriflunomide; all were mild to moderate and resolved while the patients continued treatment.

Serious infections

In the ASCLEPIOS studies, the percentage of patients who reported a serious infection was 2.5% with ofatumumab and 1.8% with teriflunomide.

The following was reported in the **ofatumumab** group: appendicitis (in 8 patients); gastroenteritis and urinary tract infection (3 patients each), influenza (2 patients); and cystitis, escherichia urinary tract infection, kidney infection, lower respiratory tract infection, neutropenic sepsis, osteomyelitis, pneumonia, upper respiratory tract infection, urosepsis and viral respiratory tract infection (1 patient each).

The following was reported in the **teriflunomide** group: appendicitis and urinary tract infection (2 patients each) and abscess of the sweat glands, campylobacter infection, cystitis, influenza pneumonia, osteomyelitis, paronychia, peritonitis, pneumonia, postoperative abscess, salpingo-oophoritis, sepsis, tickborne viral encephalitis and viral infection (1 patient each).

No opportunistic infections were reported [4].

The occurrence of severe opportunistic infections, especially John Cunningham (JC) virus infection resulting in PML, is of concern when treating long term with high-efficacy DMTs. PML has been observed in patients treated with anti-CD20 antibodies, other MS therapies and ofatumumab at doses of 300-2000 mg i.v. weekly to treat hematologic cancers (vs. 20 mg subcutaneously monthly in MS). Recently, the SmPC for dimethyl fumarate, a medium-efficacy DMT used first line, was updated with information of one fatal case in a clinical study and a number of cases in post-marketing reports [6].

There have been no reports of PML in patients treated with **ocrelizumab** for MS to date.

Severe infections, including sepsis, sometimes fatal, have been reported for **teriflunomide** in post-marketing data.

Cancer

There was no imbalance between the treatment groups in the ASCLEPIOS studies, with 5 neoplasms occurring in the **ofatumumab** treated patients vs. 4 in the **teriflunomide** treated patients. None of the malignant events were considered by the investigators to be related to study treatment, and no cluster of neoplasms were identified [4].

SPECIFIACLLY FOR TERIFLUNOMIDE

Hepatic effects

Elevations of liver enzymes have been observed in patients receiving teriflunomide. These elevations occurred mostly within the first 6 months of treatment and were reversible after treatment cessation. The recovery time varied between months and years.

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Cases of drug-induced liver injury (DILI), sometimes life-threatening, have been observed during treatment with teriflunomide. Most cases of DILI occurred with time to onset of several weeks or months after treatment initiation of teriflunomide; however, DILI can also occur with prolonged use.

Patients should be closely monitored for signs and symptoms of liver injury.

Teriflunomide therapy should be discontinued and accelerated elimination procedure considered if liver injury is suspected, and discontinuation should be considered if elevated liver enzymes (greater than 3-fold upper limit of normal [ULN]) are confirmed.

Blood pressure effects

Elevation of blood pressure may occur during treatment with teriflunomide. Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter. Blood pressure elevation should be appropriately managed before and during treatment with teriflunomide.

Haematological effects

A mean decrease affecting white blood cell (WBC) count (<15% from baseline levels, mainly neutrophil and lymphocytes decrease) was observed in placebo-controlled studies with teriflunomide, although a greater decrease was observed in some patients. The decrease in mean count from baseline occurred during the first 6 weeks; it then stabilised over time while on-treatment but at decreased levels (less than a 15% decrease from baseline). The effect on red blood cell (RBC) (<2%) and platelet counts (<10%) was less pronounced.

Alopecia

Alopecia was reported in 13.9% of patients treated with 14 mg teriflunomide versus 5.1% of patients treated with placebo. Most cases occurred during the first 6 months and with resolution in 121 of 139 (87.1%) patients treated with teriflunomide 14 mg. Discontinuation because of alopecia was 1.3% in the 14 mg teriflunomide group versus 0.1% in the placebo group in the pivotal placebo-controlled phase 3 studies.

Peripheral neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. In the pivotal placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9% (17 patients out of 898) with 14 mg teriflunomide compared to 0.4% (4 patients out of 898) with placebo. Treatment was discontinued in 5 patients with peripheral neuropathy on teriflunomide 14 mg. Recovery following treatment discontinuation was reported in 4 of these patients.

Severe skin reactions

Cases of severe skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with teriflunomide in post-marketing data.

Interactions

Concomitant drug use should be considered when treating with teriflunomide, as teriflunomide interacts with several drugs:

- Potent cytochrome P450 (CYP) and transporter inducers
- Cholestyramine or activated charcoal

- CYP2C8 substrate, such as repaglinide
- Oral contraceptives, such as ethinylestradiol and levonorgestrel
- CYP1A2 substrate, such as caffeine
- Warfarin
- Organic anion transporter 3 (OAT3) substrates such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate and zidovudine
- BCRP and/or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates

For ofatumumab, the only interactions mentioned in the SmPC are other immunosuppressive or immune-modulating therapies and vaccinations.

SPECIFICALLY FOR OFATUMUMAB

Injection-related reactions

In the ASCLEPIOS studies, injection-related reactions (systemic) were reported in 20.6% (20.2% stated in the publication [4]) of the patients treated with ofatumumab. The incidence of injection-related reactions was highest with the first injection (14.4%), decreasing significantly with subsequent injections (4.4% with second, <3% from third injection onward). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) ofatumumab-treated MS patients reported serious but not life-threatening injection-related reactions. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills and fatigue.

In the ASCLEPIOS studies, injection-site reactions (local) were reported in 10.9% of the patients treated with ofatumumab. Local reactions at the administration site were very common. Injection-site reactions were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2%) included erythema, pain, itching and swelling.

Immunoglobulins

During the course of the ASCLEPIOS studies, decrease in mean value of immunoglobulin M (IgM) (30.9% decrease after 48 weeks and 38.8% decrease after 96 weeks) was observed, and no association with risk of infections, including serious infections, was shown. In 14.3% of the patients, treatment with ofatumumab resulted in a decrease in IgM that reached a value below 0.34 g/l.

Ofatumumab was associated with a transient decrease of 4.3% in mean IgG levels after 48 weeks of treatment but an increase of 2.2% after 96 weeks.

Long term safety (≥5 years) for ofatumumab

The Medicines Council have asked specifically for data on long-term safety for ofatumumab, especially with focus on development of neutropenia, decreasing IgG levels, infections and response to vaccinations.

The main studies in the clinical development programme for ofatumumab in RMS, the ASCLEPIOS studies, were initiated in late 2016, and patients were offered to continue in the ongoing ALITHIOS study [8]. Thus, there is no data beyond five years in patients with MS and on the dose approved of ofatumumab for this indication. The ALITHIOS study is an open-label study with approximately 1703 patients being followed with the objective to monitor the long-term safety of ofatumumab. Two Danish hospitals (sites) are participating. A 3.5-year safety update is planned to be presented at the EAN congress in June 2021.

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The annual updates of the investigator brochure and the development safety update report (DSUR) (data cut-off date 21 December 2020) include a re-assessment of the benefit/risk, which is unchanged (including serious infections and PML). No cases of PML have been reported for ofatumumab to date. Both documents have been shared with the regulators.

Vaccination
All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to the initiation of ofatumumab for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to the initiation of ofatumumab for inactivated vaccines.

The safety of immunisation with live or live-attenuated vaccines following ofatumumab therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion. The median time to B-cell recovery to the lower limit of normal (LLN, defined as 40 cells/µl) or to the baseline value is 24.6 weeks post treatment discontinuation based on data from the ASCLEPIOS studies.

Ofatumumab may interfere with the effectiveness of inactivated vaccines. Currently, there is no data on the concomitant use of ofatumumab with inactivated vaccines, including influenza vaccines and the mRNA or the replication-deficient viral vector vaccines against SARS-CoV-2. Three studies with the Pfizer and Moderna mRNA vaccines are planned in ofatumumab-treated MS patients [20-22]. In addition, response to vaccination is investigated in the open-label extension (OLE) study, ALITHIOS [8], and a study to assess response to influenza vaccine in MS patients treated with ofatumumab is ongoing [22].

For information, live clinical studies have shown that vaccinations with inactivated neoantigen (first vaccination) or recall antigen (re-exposure) were safe and effective during teriflunomide treatment. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

Safety in relation to fertility, pregnancy and lactation is addressed in section 5.3.1.

Overall, the incidence of AEs and SAEs was similar for ofatumumab and teriflunomide in ASCLEPIOS I and II.

The overall proportion of patients with infections was similar in the ofatumumab and teriflunomide treatment groups. In the ASCLEPIOS studies, the percentage of patients who reported a serious infection was 2.5% with ofatumumab and 1.8% with teriflunomide. No opportunistic infections, including PML, cryptococcal infections or reactivation of hepatitis were reported.

Apart from infections, local and systemic injection-related reactions were the most frequent adverse drug reactions. The incidence of systemic injection-related reactions was highest with the first injection (14.4%), decreasing significantly with subsequent injections and were mostly (99.8%) mild to moderate in severity.

Long term data for ofatumumab is limited. An open-label follow-up study, ALITHIOS [8], is ongoing, and a 3.5-year safety update is planned to be presented at the EAN congress in June 2021. [redacted]

Some adverse reactions for teriflunomide require close monitoring, such as elevated liver enzymes, increased blood pressure and decreased white blood cell count. Cases of life-threatening liver injury, as well as fatal cases or severe

skin reactions, have been reported post-marketing, and concomitant medication must be considered due to several drug-drug interactions with teriflunomide.

Annualised Relapse Rate

Ofatumumab reduced the ARR by 0.128 (95% CI-0.163;-0.093), p<0.0001 vs. teriflunomide.

A reduction in relapse rates has a meaningful impact on patients, both due to a reduction in the short-term negative effects of their occurrence and due to the significant and consistent correlation between clinical relapses and longer-term disability worsening [23-25].

Ofatumumab was statistically significantly more effective in lowering the ARR vs. teriflunomide, and the difference between the treatments meets the minimal clinically important difference of 0.1 as defined in the protocol [17].

The results are shown in Table 22, Appendix 7.4 and the forest plots are shown in Appendix 7.6.

Cognitive function

[redacted]

In conclusion, there was no difference in effect on the cognitive function measured by the SDMT score.

The results are shown in Table 22, Appendix 7.4 and the forest plots are shown in Appendix 7.6.

Quality of life

[redacted]

In conclusion, mean changes from baseline in the EQ-5D utility score and the EQ-5D VAS score were statistically significantly in favour for ofatumumab vs. teriflunomide.

The results are shown in Table 14 and Table 15, Appendix 7.3 and Table 22, Appendix 7.4 and the forest plots are shown in Appendix 7.6.

5.1.4 Conclusion and discussion for clinical question 1

Ofatumumab was associated with reductions in the risk of disability progression, allowing patients to maintain their physical abilities as long as possible and extend the time to SPMS as much as possible.

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A reduction in relapse rates has a meaningful impact on patients, both due to a reduction in the short-term negative effects of their occurrence and the significant and consistent correlation between clinical relapses and time to longer-term disability worsening [23-25]. In the ASCLEPIOS I and II studies, ofatumumab was associated with an adjusted ARR of 0.11 and 0.10, respectively, equivalent to one relapse in 10 years.

No effect on cognition, measured by SDMT, was observed in the ASCLEPIOS studies. However, based on discussions with Danish clinical experts in MS, significant changes in cognitive function in an RMS population upon treatment with a DMT cannot be expected over a 2-year period. Neither was effect on quality of life measurable with EQ-5D, although the scores were consistently higher for ofatumumab vs. teriflunomide.

With regard to quality of life, the mean changes from baseline in the EQ-5D utility score and the EQ-5D VAS score were statistically significantly in favour for ofatumumab.

Overall, the incidence of AEs and SAEs were similar for ofatumumab and teriflunomide in ASCLEPIOS I and II [4].

The overall proportion of patients with infections was similar in the ofatumumab and the teriflunomide treatment groups. In the ASCLEPIOS studies, the percentage of patients who reported a serious infection was 2.5% with ofatumumab and 1.8% with teriflunomide. No opportunistic infections, including PML, cryptococcal infections or reactivation of hepatitis were reported. PML is normally a concern with high-efficacy DMT; however, recently, the SmPC of dimethyl fumarate has been updated with information of one fatal case of PML in a clinical study and a number of cases (not specified) post-marketing [6].

Apart from infections, local and systemic injection-related reactions were the most frequent adverse drug reactions. The incidence of systemic injection-related reactions was highest with the first injection (14.4%), decreasing significantly with subsequent injections and were mostly (99.8%) mild to moderate in severity.

Long-term data for ofatumumab is limited. An open-label follow-up study, ALITHIOS [8], is ongoing, and a 3.5-year safety update is planned to be presented at the EAN congress in June 2021 [redacted]

Some adverse reactions for teriflunomide require close monitoring, such as elevated liver enzymes, increased blood pressure and decreased WBC count. Cases of life-threatening liver injury, as well as fatal cases or severe skin reactions have been reported post-marketing, and concomitant medication must be considered due to several drug-drug interactions with teriflunomide.

In conclusion, the ASCLEPIOS study results showed that ofatumumab was clinically and statistically more effective than teriflunomide with regard to CDP-3 and annual attack rates. EQ-5D scores were statistically significantly in favour vs. teriflunomide, and ofatumumab was generally well tolerated, with an acceptable and manageable AE profile and minimal monitoring required.

5.1.5 Considerations related to first line usage of high-efficacy DMTs like ofatumumab

Ofatumumab may be used first line according to the label and may address a medical need. Over time, a large proportion of patients with RRMS progress to SPMS [14, 26]. Despite the fact that the high-efficacy DMTs have become available during the last 13 years, there is still a real risk for disease progression for patients with RRMS. Generally, the high-efficacy DMTs are considered to have a less favourable safety profile and are reserved for patients

who have high disease activity initially or who either do not respond adequately to medium-efficacy DMTs or do not tolerate them [27].

In a Danish registry study, patients who were treated with high-efficacy DMTs as first-line treatment were matched with patients with similar demographic and disease characteristics but treated with medium-efficacy DMTs as first-line therapy. At 4 years of follow-up, the probabilities of a 6-month confirmed EDSS score worsening were 16.7% and 30.1% for high-efficacy DMTs and medium-efficacy DMTs, respectively (hazard ratio 0.53, 95% CI 0.33;0.83, p = 0.006) [10].

There is a growing consensus that the use of high-efficacy DMTs early in the disease may minimise the disease activity and the progression of the disease [28-30]. The register-based study by Buron et al show that the proportion of treatment naïve Danish MS patients starting on high-efficacy DMTs as first-line therapy is increasing each year and was 15.7% of patients in 2018 [10]; based on discussions with clinical MS experts, there seems to be a tendency that the clinician's definition of high disease activity is becoming less restrictive, resulting in more patients starting treatment directly on high-efficacy DMTs.

The ASCLEPIOS study results demonstrated that ofatumumab is more efficacious than teriflunomide and is generally well tolerated, with an acceptable and manageable AE profile and minimal monitoring required.

As a monthly self-administered treatment, ofatumumab will be the first B cell therapy accessible for all patients with RMS, providing a high-efficacy and well-tolerated treatment option. Ofatumumab therefore has the potential to shift the treatment paradigm in the RMS population more routinely towards early use of high-efficacy treatment. The latter has been associated with improvements in clinical outcome, also shown in a Danish patient population [10].

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5.2 Clinical question 2: What is the value of ofatumumab compared to ocrelizumab for patients with RMS and average high disease activity (second line treatment)?

5.2.1 Presentation of relevant studies

There are no RCTs directly comparing ofatumumab to ocrelizumab for the treatment of patient with RMS. An indirect comparison with the Bucher method is not possible, as the identified studies did not include the same comparator as a link for indirect comparison. According to the protocol from the Medicines Council, network meta-analyses should only be performed if specifically asked for in the protocol. It was therefore agreed with the Medicines Council during the dialogue meeting that the comparison between ofatumumab and ocrelizumab should be done narratively.

The comparison is based on four studies, which are pair-wise identical in design: ASCLEPIOS I and II which compared ofatumumab to teriflunomide and OPERA I and II which compared ocrelizumab to interferon beta-1a.

The study design and baseline characteristics for the four studies is summarised in Table 6.

Table 6 Study and baseline characteristics

	ASCLEPIOS I		ASCLEPIOS II		OPERA I		OPERA II	
Intervention	Ofatumumab 20 mg subcutaneously every 4 weeks, after 20 mg loading doses at days 1, 7 and 14				Ocrelizumab 600 mg intravenously every 24 weeks, administered as 300 mg intravenously on day 1 and 15 for the first dose			
Comparator	Teriflunomide 14 mg orally once daily				Interferon beta-1a (Rebif) 44 µg subcutaneously three times weekly			
Design	RCT				RCT			
Primary endpoint	ARR				ARR			
Inclusion criteria	EDSS score of 0 to 5.5. At least one relapse in the year before screening, at least two relapses in the 2 years before screening, or at least one lesion detected with the use of gadolinium enhancement on magnetic resonance imaging (MRI) in the year before randomization; and a neurologically stable condition for at least 1 month before randomization.				EDSS score between 0 and 5.5 at screening. At least two documented clinical relapses within the previous 2 years or one clinical relapse within the year before screening; magnetic resonance imaging of the brain showing abnormalities consistent with multiple sclerosis; and no neurologic worsening for at least 30 days before both screening and baseline.			
Age	18-55 years				18-55 years			
Type of MS	RRMS or SPMS with disease activity				MS, not PPMS			
Follow-up	Adjusted on the basis of a predefined overall minimum event rate. Median follow up was 1.6 years. More than 30% of patients participated in the study for more than 2 years.				96 weeks			
Baseline characteristics	**ASCLEPIOS I**		**ASCLEPIOS II**		**OPERA I**		**OPERA II**	
	OFA	TER	OFA	TER	OCR	INF	OCR	INF
n	465	462	481	474	410	411	417	418
Age, mean (year)	38.9±8.8	37.8±9.0	38.0±9.3	38.2±9.7	37.1±9.3	36.9±9.3	37.2±9.1	37.4±9.0
Women (%)	68.4	68.6	66.3	67.3	65.9	66.2	65.0	67.0
Duration of MS since diagnosis (years)	5.77±6.05	5.64±6.20	5.59±6.38	5.48±6.00	3.82±4.80	3.71±4.63	4.15±4.95	4.13±5.07
Previous DMT (% with prior experience[a])	58.9	60.6	59.5	61.8	26.2	28.6	27.1	24.7

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	ASCLEPIOS I		ASCLEPIOS II		OPERA I		OPERA II	
Number of relapses in the past year	1.2±0.6	1.3±0.7	1.3±0.7	1.3±0.7	1.31±0.65	1.33±0.64	1.32±0.69	1.34±0.73
EDSS score at baseline	2.97±1.36	2.94±1.36	2.90±1.34	2.86±1.37	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38
Absence of Gd+ T1 lesions (%)	62.6	63.4	56.1	61.4	57.5	61.9	61.0	58.6
Volume of T2 lesions (cm^3)	13.2±13.3	13.1±14.6	14.3±14.2	12.0±13.2	10.8±13.9	9.7±11.3	10.7±14.3	10.6±12.3
Normalised brain volume (cm^3)	1439±81	1442±79	1441±77	1446±77	1501±84	1499±88	1504±93	1501±91

OFA = ofatumumab, TER = teriflunomide, OCR = ocrelizumab, INF = Interferon beta-1a
[a]For OPERA I & II, refers specifically to prior experience with any DMT in the two years before screening
Abbreviations: BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; MS = multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis

The ASCLEPIOS and OPERA studies were very similar in design: they were all randomised double-dummy controlled studies, and the eligibility criteria were similar. The studies differed on duration: The duration of the ACLEPIOS studies was adjusted on the basis of a predefined overall minimum event rate. This resulted in a median follow-up time of 1.6 years, with more than 30% of patients participating in the study for more than 2 years. The OPERA studies had a fixed treatment duration of 96 weeks.

The comparators were different in the ASCLEPIOS and OPERA studies, teriflunomide and interferon beta-1a, respectively. Teriflunomide is, together with dimethyl fumarate, recommended as first choice in first-line therapy, and interferon beta-1a is recommended to be considered in first line according to the treatment recommendation for RMS by the Medicines Council [31].

The ASCLEPIOS studies and OPERA studies both had ARR as the primary endpoint. The studies differ in the definition of the secondary endpoint CDP-3/CDW-3, and this affects the results. The differences are described in detail in Table 8.

Baseline characteristics are shown in Table 6. The populations are mostly similar. However, patients in the ofatumumab studies were a little older and had longer disease duration than patients in the ocrelizumab studies, which may indicate a more advanced stage of the disease in the patients in the ASCLEPIOS studies. Furthermore, more patients (more than 70%) in the OPERA studies, compared with the ASCLEPIOS studies (about 40%), were treatment naïve, where a better response to treatment is normally expected [32].

5.2.2 Results per study

Results from the ASCLEPIOS I and II studies are described in section 5.1.2. Results from the OPERA I and II studies are described in this section.

All efficacy results are presented for the IIT populations. All safety results are presented for the safety populations.

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Confirmed disability progression at 3 months (CDP-3)

In OPERA I and II, the proportion of patients with CDP-3 was a secondary endpoint. CDP-3 was defined as an increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5), which was sustained for at least 12 weeks.

In the OPERA I study, the proportion of patients with CDP-3 was 7.6% for ocrelizumab and 12.2% for interferon beta-1a, resulting in an estimated absolute difference of -5.05% points (95% CI -7.50;-1.15), and an estimated relative difference of 0.57 (95% CI 0.37;0.90), p=0.013.

In the OPERA II study, the proportion of patients with CDP-3 was 10.6% for ocrelizumab and 15.1% for interferon beta-1a, resulting in an estimated absolute difference of -5.3% points (95% CI -8.46;-1.12), and an estimated relative difference of 0.63 (95% CI 0.42;0.92), p=0.021.

In conclusion, the risk reduction achieved with ocrelizumab vs. interferon for CDP-3 was 43.0% and 37.0% in the two studies, with statistical significance achieved in both the OPERA studies.

Results are shown in Table 20 and Table 17, Appendix 7.3.

Serious adverse events and adverse events

AEs (treatment emergent AEs, regardless of relation to study drug), SAEs, AEs leading to treatment discontinuation, and deaths in the OPERA I and II studies are summarised in Table 7 [12].

Table 7 Safety results of OPERA I and II studies

Variable	OPERA I		OPERA II	
	Ocrelizumab (N=408)	Interferon Beta-1a (N=409)	Ocrelizumab (N=417)	Interferon Beta-1a (N=417)
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes infection				
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Neoplasm	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)

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Variable	OPERA I		OPERA II	
	Ocrelizumab (N=408)	Interferon Beta-1a (N=409)	Ocrelizumab (N=417)	Interferon Beta-1a (N=417)
Death[1]	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)
Serious infection or infestation	5 (1.2)	12 (2.9)	6 (1.4)	12 (2.9)

Numbers represent the number of patients (%), safety population.

1: Deaths occurring during the studies were due to suicide (one in the ocrelizumab group in the OPERA II study and one in the interferon beta-1a group in the OPERA I study) and mechanical ileus (one in the interferon beta-1a group in the OPERA II study).

The most common AEs were infusion-related reaction, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection in patients treated with ocrelizumab and influenza-like illness, injection-site erythema, headache, urinary tract infection, and upper respiratory tract infection in patients treated with interferon beta-1a.

In section 5.1.3. the safety profiles of ocrelizumab and ofatumumab are discussed in detail.

In conclusion, the OPERA results demonstrated ocrelizumab to be generally well tolerated, compared to interferon beta-1a.

The proportion of patients experiencing an SAE is also shown in Table 20 and Table 17, Appendix 7.3.

Annualised relapse rate (ARR)

The ARR was the primary outcome in the OPERA studies.

- The ARR was defined as the number of relapses meeting the prespecified criteria that were observed per person-year of follow up.
- Definition of relapse: Relapses that were attributable to MS only in the absence of fever or infection; persisted for over 24 hours; were immediately preceded by a stable or improving neurologic state for at least 30 days; and were accompanied by objective neurologic worsening consistent with an increase of at least half a step on the EDSS, 2 points in one EDSS functional system score, or 1 point in each of two or more EDSS functional system scores (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual).
- Protocol-defined relapses were confirmed to have met the prespecified criteria defined in the protocol by a computerised algorithm. In case of inconsistencies, scorings were reviewed centrally. The final decision about the correct scores remained with the EDSS examining investigators.

In the OPERA I study, the ARR was **0.16 (95% CI 0.12;0.20)** for ocrelizumab and **0.29 (95% CI 0.24;0.36)** for interferon beta-1a, resulting in an estimated absolute difference of -0.14 (95% CI -0.193;0.079), p<0.001, and an estimated relative difference of 0.54 (95% CI 0.40;0.72), p<0.0001.

In the OPERA II study, the ARR was **0.16 (95% CI 0.12;0.20)** for ocrelizumab and **0.29 (95% CI 0.23;0.36)** for interferon beta-1a, resulting in an estimated absolute difference of -0.13 (95% CI -0.192;0.078), p<0.001,and an estimated relative difference of 0.53 (95% CI 0.40;0.71), p<0.0001.

In conclusion, ocrelizumab reduced the ARR by 46% and 47% compared to interferon beta-1a, a difference that was both statisically significant and above the minimal clinically important difference of 1.0 [17].

Results are shown in Table 20 and Table 17, Appendix 7.3.

Cognitive function

According to the protocol, SDMT was measured in the OPERA I and II studies. However, the results have not been published.

Quality of life

In the OPERA I and II studies, the change from baseline to week 96 in the physical component summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, on which scores range from 0 to 100, and higher scores indicate better physical health–related quality of life) was assessed.

In the OPERA I study, the mean change from baseline in SF-36 was 0.04 (95% CI -0.86;0.93) for ocrelizumab and -0.65 (95% CI -1.59;0.28) for interferon beta-1a, resulting in an estimated absolute difference of 0.69 (95% CI -0.41;1.80), p=0.2853.

In the OPERA II study, the mean change from baseline in SF-36 was 0.33 (95% CI -0.55;1.20) for ocrelizumab and -0.83 (95% CI -1.76;0.09) for interferon beta-1a, resulting in an estimated absolute difference of 1.16 (95% CI 0.05;2.27), p=0.0662.

In conclusion, changes in the SF-36 score from baseline were small for both ocrelizumab and interferon beta-1a, numerically increasing for ocrelizumab and decreasing for interferon beta-1a in both OPERA I and II, but not reaching a statistically significant difference.

Results are shown in Table 20 and Table 17, Appendix 7.3.

5.2.3 Comparative analyses

The comparative analysis between ofatumumab and ocrelizumab is done narratively.

There are no RCTs directly comparing ofatumumab to ocrelizumab for the treatment of patients with RMS. An indirect comparison with the Bucher method is not possible, as the identified studies did not include the same comparator as a link for indirect comparison. According to the protocol from the Medicines Council, network meta-analyses should only be performed if specifically asked for in the protocol. It was therefore agreed with the Medicines Council during the dialogue meeting that the comparisons between ofatumumab and ocrelizumab should be done narratively.

Differences between the ASCLEPIOS studies and the OPERA studies are described in section 5.2.1.

Confirmed Disability Progression at 3 months (CDP-3)

The definitions of CDP-3 differed somewhat in the two studies, as described in Table 8.

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Table 8 Definitions of CDP-3 in the ASCLEPIOS and OPERA studies [4, 12]

	ASCLEPIOS studies	OPERA studies
EDSS change defining progression	• An increase of at least 0.5 points in EDSS score from a baseline score of ≥5.5, • An increase of at least 1 point from a baseline score of 1 to 5, or • An increase of at least 1.5 points from a baseline score of 0	• An increase of at least 0.5 points in EDSS score from a baseline score of >5.5 or • An increase of at least 1 point from a baseline score of 0 to 5.5
Baseline EDSS	The last EDSS assessment prior to the first dose of study medication.	The mean (without rounding) of the EDSS scores at the screening and baseline visits
Time sustained for confirmation	≥90 day	≥84 days

The proportion of patients with CDP-3 (pooled studies analysis) were 10.9% for ofatumumab and 9.1% for ocrelizumab [4, 12].

Ofatumumab reduced the risk of CDP-3 by 34.5% vs. teriflunomide, and ocrelizumab reduced the risk of CDP-3 by in 39.7% vs. interferon beta-1a.

Even if the definition of CDP-3 differed in the ASCLEPIOS and OPERA studies, the results seem similar, and the conclusion is thus that ofatumumab and ocrelizumab seem to have similar effect when it comes to CDP-3.

The results are shown in Table 22 and Table 23, Appendix 7.4, and the forest plots are shown in Appendix 7.6.

Adverse reactions

Serious adverse events

In the ASCLEPIOS studies, 9.1% of patients treated with ofatumumab experienced an SAE [4]. In the OPERA studies, the proportion of patients with an SAE for patients treated with ocrelizumab was 6.9% [12].

The results are similar when considering that the results are from different studies. The difference does not exceed the minimal relevant important difference of 3% points as defined in the protocol [17].

The results are shown in Table 22 and Table 23, Appendix 7.4, and the forest plots are shown in Appendix 7.6.

General safety profile

The Medicines Council has asked for a review of the safety profiles of ofatumumab and teriflunomide based on both clinical data and the SmPCs. A comprehensive overview of the safety information in the SmPCs is included in Appendix 7.5.

Unless otherwise stated, the information in this section is based on the approved SmPCs for ocrelizumab and ofatumumab [3, 9].

Drug characteristics

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Ocrelizumab and ofatumumab are both anti-CD20 monoclonal IgG1 antibodies but with some differences, as shown in Table 9.

Table 9 Differences between ocrelizumab and ofatumumab

	Ocrelizumab	Ofatumumab
Structure [3, 9]	Humanized	Fully human
Type of antibody [3, 9]	IgG1	IgG1
Immunogenicity [32]	++	+
Binding sites [33]	Binds to the large extracellular loop of the CD20 molecule on B cells	Binds to the small loop and to a part of the large loop of the CD20 molecule on B cells, that is completely distinct from the binding site of ocrelizumab, and closer to the cell membrane
Primary mode of action [32]	ADCC > CDC	CDC > ADCC
Administration [3, 9, 34-36]	Intravenously More systemic exposure	Subcutaneously Direct to lymph nodes
B-cell repletion time [3, 9]	72 weeks	24.6 weeks
Abbreviations: ADCC = antibody-dependent cell cytotoxicity; CDC = complement-dependent cytotoxicity; IgG = immunoglobulin G, MOA = mode of action		

The different characteristics between the two drugs may lead to differences in the safety profiles of the drugs.

Administration

Ocrelizumab is administered i.v., initially as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion, and subsequently as a single 600 mg i.v. infusion every 6 month.

To reduce the frequency and severity of infusion related reactions (IRRs), the following two pre-medications must be administered:

- 100 mg i.v. methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion
- antihistamine approximately 30-60 minutes prior to each ocrelizumab infusion
- In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each ocrelizumab infusion.

Each infusion should be given over approximately 2 to 3.5 hours.

Ofatumumab is administered subcutaneously with initial low dosing of 20 mg at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4. Ofatumumab can be self-administered by the patient or by a caregiver after an initial instruction by a health care professional (week 0), and no pre-medication is required.

Contraindications

Ocrelizumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, patients with current active infection, patients in a severely immunocompromised state and patients with known active malignancies.

The same contraindications apply to **ofatumumab**, except that for infections, ofatumumab is contraindicated only for patients with severe active infection until resolution.

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Special warnings and precautions

For **ocrelizumab**, the special warnings and precautions mentioned in the SmPCs are listed in Table 10.

Table 10 Special warnings and precautions for ocrelizumab and ofatumumab

Ocrelizumab	Ofatumumab
Traceability Infusion-related reactions Hypersensitivity reactions Infection • Progressive multifocal leukoencephalopathy • Hepatitis B reactivation • Late neutropenia Malignancies Treatment of severely immunocompromised patients Vaccinations • Median time for B-cell repletion was **72.0** weeks	Traceability Injection-related reactions Infection • Progressive multifocal leukoencephalopathy • Hepatitis B reactivation Malignancies Treatment of severely immunocompromised patients Vaccinations • Median time for B-cell repletion was **24.6** weeks

Most common adverse events

For **ocrelizumab**, very common (≥1/10) adverse reactions, as described in the SmPC, were upper respiratory tract infection, nasopharyngitis, influenza, blood IgM decreased and IRRs. Common (≥1/100 to <1/10) adverse reactions were sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis, cough, catarrh, blood IgG decreased and neutropenia. Late onset of neutropenia has been reported in the post-marketing setting. In addition, in the OPERA studies, headache and urinary tract infection were reported as being common [12].

For **ofatumumab**, very common (≥1/10) adverse reactions, as described in the SmPC, were upper respiratory tract infections, systemic injection-related reactions, injection-site reactions and urinary tract infections. Common (≥1/100 to <1/10) adverse reactions were oral herpes and blood IgM decreased. In addition, nasopharyngitis and headache were seen in at least 10% of those treated with ofatumumab [4].

Adverse reactions of special interest

Infusion-related reactions (IRR), **ocrelizumab**

Across the RMS and PPMS studies, symptoms associated with IIRs included but are not limited to pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea and tachycardia. IRRs were managed with infusion adjustments and treatment of symptoms. In controlled studies, there were no fatal IRRs. In addition, symptoms of IRR in the post-marketing setting included anaphylaxis.

In the OPERA clinical studies, IRR was the most common AE in patients treated with ocrelizumab with an overall incidence of 34.3%. The incidence of IRRs was the highest during the first dose, infusion 1 (27.5%), and decreased over time to <10% at dose 4. The majority of the IRRs were mild to moderate. In total, 21,7% and 10.1% of ocrelizumab-treated patients experienced mild and moderate IRRs, respectively, while 2.4% experienced severe IRRs and 0.1% experienced life-threatening IRRs.

Injection-related reactions, **ofatumumab**

In the ASCLEPIOS studies, injection-related reactions (systemic) were reported in 20.6% of patients (20.2% stated in the publication [4]) treated with ofatumumab. The incidence of injection-related reactions was the highest with the first injection (14.4%), decreasing significantly with subsequent injections (4.4% with second, <3% from third injection onward). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Two (0.2%) ofatumumab-treated MS patients reported serious but not life-threatening injection-related reactions. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills and fatigue.

In the ASCLEPIOS studies, injection-site reactions (local) were reported in 10.9% of patients treated with ofatumumab. Local reactions at the administration site were very common. Injection-site reactions were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2%) included erythema, pain, itching and swelling.

Infections

In the OPERA studies, infections occurred in 58.5% of patients receiving **ocrelizumab**. Serious infections occurred in 1.3% of patients receiving ocrelizumab.

In the RMS clinical studies, 39.9% of ocrelizumab-treated patients experienced an upper respiratory tract infection and 7.5% experienced a lower respiratory tract infection. The respiratory tract infections reported in patients treated with ocrelizumab were predominately mild to moderate (80%-90 %). In the ocrelizumab-treated patients, herpes zoster was reported in 2.1%, herpes simplex in 0.7%, oral herpes in 3.0%, genital herpes in 0.1% and herpes virus infection in 0.1% of the individuals. Infections were predominantly mild to moderate in severity, and the patients recovered with treatment by standard therapies.

In the ASCLEPIOS studies, infections occurred in 51.6% of patients receiving **ofatumumab**. Serious infections occurred in 2.5% of patients receiving ofatumumab.

Upper respiratory tract infections were the most frequent infections. Among ofatumumab-treated patients, 39.4% experienced upper respiratory tract infections. The infections were predominantly mild to moderate in intensity and mostly consisted of nasopharyngitis, upper respiratory tract infection and influenza. Urinary tract infections were very common (≥1/10) while oral herpes was common (≥1/100 to <1/10).

Serious infections

In the OPERA studies, the percentage of patients who reported a serious infection was 1.3% with **ocrelizumab**. The following was reported in the ocrelizumab group: appendicitis (in 3 patients), cellulitis (2 patients), pyelonephritis (2 patients), and biliary sepsis, device-related infection, herpes simplex infection, pneumonia and upper respiratory tract infection (in 1 patient each). No opportunistic infections were reported [12].

In the ASCLEPIOS studies, the percentage of patients who reported a serious infection was 2.5% with **ofatumumab**. The following was reported in the ofatumumab group: appendicitis (in 8 patients), gastroenteritis and urinary tract infection (3 patients each), influenza (2 patients) and cystitis, escherichia urinary tract infection, kidney infection, lower respiratory tract infection, neutropenic sepsis, osteomyelitis, pneumonia, upper respiratory tract infection, urosepsis and viral respiratory tract infection (1 patient each). No opportunistic infections were reported [4].

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Considering that the results derive from four different studies, the proportions of patients experiencing a serious infection with ocrelizumab and ofatumumab are considered to be similar.

The occurrence of severe opportunistic infections, especially JC virus infection resulting in PML is of concern when treating long term with high-efficacy DMTs. PML has been observed in patients treated with anti-CD20 antibodies, other MS therapies, and ofatumumab at doses of 300-2000 mg i.v. weekly to treat hematologic cancers (vs. 20 mg subcutaneously monthly in MS). Recently, the SmPC for dimethyl fumarate, a medium-efficacy DMT used first line, was updated with information of one fatal case in a clinical study and a number of cases reported in the post-marketing setting [6].

There have been no reports of PML in patients treated with **ocrelizumab** for MS in clinical studies to date. Eight cases of PML (as of September 2019) have been described in post-marketing surveillance of ocrelizumab, seven of which occurred after switching from natalizumab or fingolimod, most likely due to a carry-over effect; however, the most recent case was in a 78-year-old patient treated with ocrelizumab as a first-line therapy [32, 33].

There have been no reports of PML in patients treated with **ofatumumab** for MS.

Hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies, which in some cases resulted in fulminant hepatitis, hepatic failure and death. Hepatitis B virus screening should be performed in all patients before initiation of treatment with ocrelizumab or ofatumumab.

Neutropenia

In the OPERA studies, a decrease in neutrophils <LNN was observed in 14.7% of **ocrelizumab** treated patients. Although some cases were Grade 3 or 4, the majority of the cases were Grade 1 or 2. Cases of late onset of neutropenia have been reported at least 4 weeks after the latest ocrelizumab infusion. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Occurrence of neutropenia after treatment with **ofatumumab** is not mentioned in the SmPC; however, it is addressed in the Risk Management Plan for ofatumumab as a potential risk [1].

Immunoglobulins

Treatment with **ocrelizumab** resulted in a decrease in total immunoglobulins over the controlled period of the studies, mainly driven by reduction in IgM. Clinical study data from ocrelizumab studies have shown an association between decreased levels of IgG (and less so for IgM or IgA) and serious infections [9].

During the course of the ASCLEPIOS clinical studies, a decrease in the mean value of IgM (30.9% decrease after 48 weeks and 38.8% decrease after 96 weeks) was observed and no association with risk of infections, including serious infections, was shown. In 14.3% of the patients, treatment with **ofatumumab** resulted in a decrease in IgM that reached a value below 0.34 g/l. Ofatumumab was associated with a transient decrease of 4.3% in mean IgG levels after 48 weeks of treatment but an increase of 2.2% after 96 weeks.

Cancer

An increased number of malignancies (including breast cancers) have been observed in clinical studies in patients treated with **ocrelizumab**, compared to control groups. However, the incidence was within the background rate expected for an MS population [9].

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There was no imbalance between treatment groups in the ASCLEPIOS studies, with 5 neoplasms occurring in the **ofatumumab** treated patients vs. 4 in the teriflunomide treated patients. None of the malignant events were considered by the investigators to be related to study treatment, and no cluster of neoplasms was identified [4].

Long-term safety (≥5 years) for ofatumumab
The Medicines Council have asked specifically for data on the long-term safety of ofatumumab, especially with a focus on the development of neutropenia, decreasing IgG levels, infections and response to vaccinations.

The main studies in the clinical development programme for ofatumumab in RMS, the ASCLEPIOS studies, were initiated in late 2016, and patients were offered to continue in the ongoing ALITHIOS study [8]. Thus, there is no data beyond five years in patients who have MS and are on the approved dose of ofatumumab for this indication. The ALITHIOS study is an open-label study with approximately 1703 patients being followed with the objective to monitor the long-term safety of ofatumumab. Two Danish sites are participating. A 3.5-year safety update is planned to be presented at the EAN congress in June 2021.

The annual updates of the investigator brochure and the DSUR (data cut-off date 21 December 2020) include a re-assessment of the benefit/risk, which is unchanged (including serious infections and PML). No cases of PML have been reported for ofatumumab to date. Both documents have been shared with the regulators.

Five-year follow up for patients in the OPERA studies are available from an OLE study [37]. In total, 623 patients who were assigned to ocrelizumab in the OPERA studies completed OLE. The efficacy of ocrelizumab was maintained, and the safety profile was similar to what was seen in the OPERA studies. Two potentially serious opportunistic infections were reported in the OLE period (original treatment allocation was not specified); both patients recovered with treatment by standard therapies (systemic Pasteurella infection in a patient with RMS following a cat bite; enterovirus-induced fulminant hepatitis in a diabetic patient with RMS, resulting in liver transplantation). As of the end of April 2019, no cases of PML were identified. Over 5 study years, in the pooled OPERA study population, a reduction in serum immunoglobulin levels was observed. At baseline, the number (%) of patients with Ig concentrations below the LLN were 7 (0.5%) for IgG, 17 (1.2%) for IgA and 7 (0.5%) for IgM. Over 5 study years, for the majority of the patients, Ig levels remained above the LLN; the number (%) of patients with a decrease below the LLN at year 5 was 33 (5.4%) for IgG, 31 (5.1%) for IgA and 164 (29.5%) for IgM.

Based on the difference in the characteristics of ofatumumab and ocrelizumab, and the possibly more favourable safety profile of ofatumumab in the phase III studies, it could be expected that the long-term safety profile (>5 years) of ofatumumab may also be more favourable compared to that of ocrelizumab.

Vaccination
All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to the initiation of ofatumumab for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to the initiation of ofatumumab for inactivated vaccines.

The safety of immunisation with live or live-attenuated vaccines following ofatumumab therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion. The median time to B-cell recovery to the LLN (defined as 40 cells/µl) or the baseline value is 24.6 weeks post treatment discontinuation based on data from the ASCLEPIOS studies.

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Ofatumumab may interfere with the effectiveness of inactivated vaccines. Currently, there is no data on the concomitant use of ofatumumab with inactivated vaccines, including influenza vaccines and the mRNA or the replication-deficient viral vector vaccines against SARS-CoV-2.

Three studies with the Pfizer and Moderna mRNA vaccines are planned in ofatumumab treated MS patients [20-22]. In addition, response to vaccination is investigated in the OLE study, ALITHIOS [8], and a study to assess response to influenza vaccine in MS patients treated with ofatumumab is ongoing [38].

For ocrelizumab, a randomised open-label study in RMS patients was conducted. The percentage of patients with a positive response to tetanus vaccine at 8 weeks after vaccination was 23.9% in the ocrelizumab group compared to 54.5% in the control group (no DMT except interferon-beta). The percentage of patients with seroprotective titers against five influenza strains ranged from 20.0%−60.0% and 16.7%−43.8% pre-vaccination, and at 4 weeks post vaccination, from 55.6%−80.0% in patients treated with ocrelizumab and 75.0%−97.0% in the control group, respectively. The results suggest that the use of standard non-live vaccines remains a consideration while on ocrelizumab [39].

The faster B-cell repletion for ofatumumab (72 weeks for ocrelizumab vs. 24.6 for ofatumumab) is highly relevant for the safety in relation to fertility, pregnancy and lactation. This is addressed in Section 5.3.1.

In conclusion, ocrelizumab and ofatumumab are both anti-CD20 antibodies but have different characteristics, which may result in different safety profiles.

Overall, the incidence of AEs and SAEs were similar for ocrelizumab and ofatumumab across the OPERA and ASCLEPIOS studies.

The overall proportion of patients with infections was similar in the ofatumumab- and the ocrelizumab-treated patients across the studies, including for serious infections. Upper respiratory tract infections were the most frequent infections and were predominately mild or moderate.

No opportunistic infections, including PML, cryptococcal infections or reactivation of hepatitis were reported in the clinical studies. Eight cases of PML (as of September 2019) have been described in post-marketing surveillance of ocrelizumab, of which seven most likely are due to a carry-over effect from other DMTs, and one occurred in a 78-year-old patient treated with ocrelizumab as first-line therapy [32, 33].

There are fewer adverse drug reactions listed for ofatumumab vs. ocrelizumab in the respective SmPCs. Neutropenia, including late cases of neutropenia, and decrease of blood IgG are both described for ocrelizumab but not for ofatumumab. Ocrelizumab is contraindicated in 'current active infection', whereas the contraindication for ofatumumab is limited to 'severe active infection until resolution' [3, 9].

Administration-related reactions were very common for both ocrelizumab and ofatumumab. For ocrelizumab, more than one third of patients, 34.3%, experienced an IRR. IRRs were managed with infusion adjustments and treatment of symptoms. The incidence was highest with the first injection (27.5%) and decreased over time. The majority of the cases were mild to moderate, while 2.4% experienced severe IRRs and 0.1% experienced life-threatening IRRs.

For ofatumumab, the incidence of local injection-related reactions was 10.9% and all were mild to moderate in severity and non-serious in nature. The incidence of systemic injection-related reactions was highest with the first

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injection (14.4%) and decreased significantly with subsequent injections and were mostly (99.8%) mild to moderate in severity.

Vaccination-studies are ongoing with ofatumumab. A vaccination study in ocrelizumab-treated patients showed that there is a decreased antibody response to inactivated vaccines in patients treated with ocrelizumab; however, the authors concluded that the results suggest that the use of standard inactivated vaccines remains a consideration while on ocrelizumab [39].

Long-term data for ofatumumab is limited. An open-label follow-up study, ALITHIOS [8], is ongoing, and a 3.5-year safety update is planned to be presented at the EAN congress in June 2021. [redacted]

The faster B-cell repletion for ofatumumab (72 weeks for ocrelizumab vs. 24.6 for ofatumumab) is highly relevant for safety in relation to fertility, pregnancy and lactation. This is addressed in Section 5.3.1.

Annualised Relapse Rate

The annualised relapse rate was 0.11 (95% CI 0.09;0.14) and 0.10 (0.08;0.13) for ofatumumab in ASCLEPIOS I and II, and 0.16 (95% CI 0.12;0.20) for ocrelizumab in both OPERA studies.

Ofatumumab decreased the ARR by 0.128 vs. teriflunomide (95% CI -0.163;-0.093, p<0.0001) and ocrelizumab decreased the ARR by 0.136 vs. interferon beta-1a (95% CI -0.188;-0.083, p<0.0001).

In conclusion, ofatumumab and ocrelizumab have similar efficacy in terms of ARR.

The results are shown in Table 18 to Table 21, Appendix 7.3 and in Table 22 and Table 23, Appendix 7.4, and the forest plots are shown in Appendix 7.6.

Cognitive function

No comparison is possible, as there are no published data for ocrelizumab.

Quality of life

No numerical comparison between effect on quality of life is possible, since two different measures were used. EQ-5D was used in the ASCLEPIOS studies for ofatumumab, and SF-36 was used in the OPERA studies for ocrelizumab [4, 12].

[redacted]

For ocrelizumab, the changes from baseline for SF-36 was 0.04 (95% CI -0.86;0.93) in OPERA I and 0.33 (95% CI -0.55;1.20) in OPERA II. The changes were numerically higher for ocrelizumab vs. interferon beta-1a but not statistically significant.

In conclusion, changes in quality of life were measured differently in the ASCLEPIOS and OPERA studies. In the ASCLEPIOS studies, EQ-5D was used and in the OPERA studies SF-37 was used. Both ofatumumab and ocrelizumab

showed numerically better effect vs. the comparators (teriflunomide and interferon beta-1a, respectively), but statistical significance was achieved only for ofatumumab vs. teriflunomide.

The results are shown in Table 18 to Table 21, Appendix 7.3 and Table 22 and Table 23, Appendix 7.4, and forest plots are shown in Appendix 7.6.

5.2.4 Conclusion and discussion for clinical question 2

Based on the narrative comparison, there was no difference between ofatumumab and ocrelizumab with respect to efficacy related to CDP-3 and ARR. Effect on quality of life was measured differently in the ASCLEPIOS and OPERA studies; however, mean changes from baseline in the EQ-5D utility score and the EQ-5D VAS score were statistically significantly in favour of ofatumumab in the ASCLEPIOS studies.

Comparison of efficacy on cognition was not possible due to lack of published data for ocrelizumab.

Ocrelizumab and ofatumumab are both anti-CD20 monoclonal IgG1 antibodies but with some differences in dosing, administration, structure, binding sites, mode of action and repletion time (see Table 9) [3, 9, 32, 33], all of which may affect the safety of the drugs.

Overall, the incidence of AEs and SAEs were similar for ofatumumab and ocrelizumab. No opportunistic infections, including PML, cryptococcal infections or reactivation of hepatitis were reported in the clinical studies. Eight cases of PML have been reported in the post-marketing setting with ocrelizumab; seven were in patients who had been treated with other DMT (a carry-over effect is suspected), and one occurred in a 78-year-old treatment-naïve patient.

Ofatumumab may have a more favourable safety profile when compared with ocrelizumab: pre-medication is required in relation to infusions of ocrelizumab to minimise infusion-related reactions, and according to the SmPCs, neutropenia, including late cases, and decrease in IgG are adverse drug reactions exclusively for ocrelizumab. In addition, ocrelizumab is contraindicated for patients with current active infection, whereas ofatumumab is contraindicated only in patients with severe active infection until resolution.

Long-term data for ofatumumab is limited. An open-label follow-up study, ALITHIOS [8], is ongoing, and a 3.5-year safety update is planned to be presented at the EAN congress in June 2021. [redacted]

As a monthly self-administered treatment, ofatumumab would be the first B cell therapy accessible for all patients with RMS, providing a high-efficacy and well-tolerated treatment option for all patients, including those for whom i.v. infusion therapies are unsuitable for various reasons. At the same time, ofatumumab has the potential to reduce the burden associated with the increasing use of infusion therapies, which is even more critical under the current capacity constraints imposed by the COVID-19 pandemic.

In contrast to ocrelizumab, which is administered in hospital via infusion lasting several hours, ofatumumab will be provided in pre-filled auto-injector pens for subcutaneous injection, intended for monthly self-administration at home by patients or their carers after an initial instruction by a health care professional (week 0). It is considered that the introduction of a subcutaneous high-efficacy B cell therapy will significantly reduce the burden and capacity issues associated with the i.v. administration of ocrelizumab and other high-efficacy DMTs.

During the ongoing COVID-19 pandemic at the time of this submission, the possibility to administer ofatumumab at home may further enable patients with MS to access a high-efficacy treatment without being subjected to an increased risk of infection both during the journey to the hospital and in the hospital.

In conclusion, based on a narrative comparison across studies, ofatumumab and ocrelizumab seem to be equally efficacious, and ofatumumab may have a better safety profile compared to ocrelizumab. It is considered that the introduction of a subcutaneous high-efficacy B cell therapy will significantly reduce the burden and capacity issues associated with the i.v. administration of ocrelizumab and other high-efficacy DMTs.

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5.3 Other considerations

5.3.1 Pregnancy and use of ofatumumab

As a large part of MS patients are women of childbearing potential, it is important to consider the treatment options in patients who wish to become pregnant, are pregnant or are breast feeding.

Table 11 provides an overview of the recommendations in the SmPCs for teriflunomide, ofatumumab and ocrelizumab [3, 9, 11].

Table 11 Recommendations in the SmPCs for fertility, pregnancy and lactation

	Teriflunomide	Ofatumumab	Ocrelizumab
Fertility	Teriflunomide may cause serious birth defects when administered during pregnancy. Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. For women receiving teriflunomide treatment, who wish to become pregnant, the medicinal product **should be stopped**, and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l.	Women of childbearing potential should use effective contraception while receiving Kesimpta and for **6 months** after the last administration of Kesimpta.	Women of childbearing potential should use contraception while receiving Ocrevus and for **12 months** after the last infusion of Ocrevus.
Pregnancy	Teriflunomide is **contraindicated** in pregnancy.	Treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.	Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.
Lactation	Teriflunomide is **contraindicated** during breast-feeding.	The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, ofatumumab could be used during	Women should be advised to discontinue breast-feeding during Ocrevus therapy.

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		breast-feeding if clinically needed. However, if the patient was treated with ofatumumab up to the last few months of pregnancy, breast-feeding can be started immediately after birth.	

Teriflunomide may cause serious birth defects when administered during pregnancy and **should be stopped**, and an accelerated elimination procedure is recommended in order to more rapidly achieve a concentration below 0.02 mg/l. Teriflunomide is contraindicated during pregnancy and breast-feeding and should be stopped for women who wish to become pregnant.

Ofatumumab and ocrelizumab are both B-cell therapies but differ significantly when it comes to use in relation to pregnancy. Contraception should be used for **12 months** after stopping ocrelizumab and only **6 months** after stopping ofatumumab. Both drugs should be avoided during pregnancy, unless the potential benefit to the mother outweighs the potential risk to the foetus. Ocrelizumab should be discontinued during breastfeeding, while ofatumumab can be administered after the first few days following birth.

Use of B-cell therapies during pregnancy and lactation may increase the risk of B-cell depletion in utero, transient peripheral B-cell depletion and lymphocytopenia in infants after birth [1]. The difference in time where contraception is required is due to differences in time to B-cell repletion. For ofatumumab, data from the ASCLEPIOS studies indicate a median time to B-cell recovery to the LLN or baseline value of 24.6 weeks post treatment discontinuation [3]. For ocrelizumab, the median time for B-cell repletion was 72 weeks [9].

In conclusion, due to a faster B-cell repletion time vs. ocrelizumab (24.6 vs. 72 weeks), ofatumumab offers more flexibility to women of childbearing potential, with a period of 6 months between the last administration and stopping contraception vs. 12 months for ocrelizumab, and with the possibility to continue treatment during breastfeeding.

5.3.2 Effect of ofatumumab on the following treatment lines

Switch from ofatumumab to other therapy for MS could be relevant in case of lack of efficacy of ofatumumab, for tolerability issues, or if the patient wishes to become pregnant. The data on switching from ofatumumab to another DMT is limited. In principle, all other DMTs can be considered; however, it would be expected that moderate-efficacy DMTs, such as teriflunomide or dimethyl fumarate, and interferon would have less effect than high-efficacy DMTs, such as ocrelizumab, natalizumab, fingolimod and cladribine.

The concern when switching from a CD20 antibody is the B-cell depletion induced by ofatumumab. Before patients who have been treated with B-cell therapy for MS can start another therapy, it is essential that the B-cells have repleted to normal levels (i.e. above the LLN) [40].

For **ofatumumab**, data from the ASCLEPIOS studies indicate a fast B-cell recovery, with a median time to B-cell recovery to the LLN or the baseline value being 24.6 weeks post treatment discontinuation [3], and at week 60, repletion was 84.6% and 97.4% for ASCLEPIOS I and II, respectively [1].

For **ocrelizumab**, the median time for B-cell repletion/recovery was slower, 72 weeks. 10% of all patients still did not have their B-cells repleted to LLN or baseline by approximately 2.5 years after the last infusion [9].

With ocrelizumab, it is advisable to wait a minimum of 6 months before switching to another drug, as long as the total lymphocyte count is below the normal range [40]. Based on the faster repletion time for ofatumumab, it could be expected that the time before switching to another drug could be shorter. However, until ofatumumab has been used widely, close monitoring of patients in the months after medication switching is recommended to identify any AEs.

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7. Appendix

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7.1 Literature search

Table 12 Literature search inclusion and exclusion criteria for clinical question 2

In- and exclusion criteria	
Inclusion criteria:	Population: RMS
	Interventions: ofatumumab or ocrelizumab
	Comparators: not defined
	Outcomes: CDP-3, annual attack rate, SDMT, MSQoL54 or other QoL measures, adverse events
	Setting: Peer-reviewed publication
	Study design: Randomised controlled trial (RCT)
	Language restrictions: English and Danish
	Other search limits or restrictions: Treatment duration during the controlled phase of a study of at least one year
Exclusion criteria:	Population: Not RMS
	Interventions: Other than ofatumumab or ocrelizumab
	Comparators: not defined
	Outcomes: not including one or more of the outcomes mentioned under inclusion criteria
	Setting: other than peer-reviewed publication
	Study design: not RCT
	Language restrictions: other than English and Danish
	Other search limits or restrictions: Treatment duration during the controlled phase of a study of less than one year

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The following publications/studies were excluded during the systematic literature review.

Table 13 List of studies excluded based on full-text read

Reference	Reason for exclusion
Siddiqui MK, Khurana IS, Budhia S, Hettle R, Harty G, Wong SL. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis. Curr Med Res Opin 2018; 34 (8): 1361-1371.	Network meta-analysis. No additional relevant studies, endpoints or comparisons.
Xu X, Chi S, Wang Q, Li C, Xu B, Zhang J, et al. Efficacy and safety of monoclonal antibody therapies for relapsing remitting multiple sclerosis: A network meta-analysis. Mult Scler Relat Disord 2018; 25: 322-328.	Network meta-analysis. No additional relevant studies, endpoints or comparisons.
Barkhof F, Kappos L, Wolinsky JS, Li DKB, Bar-Or A, Hartung HP, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. Neurology 2019; 93 (19): e1778-e1786.	Reports pooled results from the OPERA studies. No additional relevant studies or endpoints.
Berardi A, Siddiqui MK, Treharne C, Harty G, Wong SL. Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing-remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches. Curr Med Res Opin 2019; 35 (8): 1371-1378.	Indirect treatment comparison. No additional relevant studies, endpoints or comparisons.
McCool R, Wilson K, Arber M, Fleetwood K, Toupin S, Thom H, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. Mult Scler Relat Disord 2019; 29: 55-61.	Network meta-analysis. No additional relevant studies, endpoints or comparisons.
Turner B, Cree BAC, Kappos L, Montalban X, Papeix C, Wolinsky JS, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. J Neurol 2019; 266 (5): 1182-1193.	Reports results from the OPERA studies in sub-groups. No relevant endpoints.
Hauser SL, Arnold DL, Bar-Or A, Brochet B, Naismith RT, Traboulsee A, et al. Five-years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. Neurology 2020; 95 (13): e1854-e1867.	Reports results from the OPERA open-label extension study. No additional relevant efficacy endpoints.

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7.2 Main characteristics of included studies

Table 14 Main study characteristics for ASCLEPIOS I

ASCLEPIOS I	
Study name	ASCLEPIOS I
NCT numbers	NCT02792218
Objective	To compare the efficacy and safety of ofatumumab administered s.c. every 4 weeks versus teriflunomide administered orally once daily in patients with relapsing multiple sclerosis
Publications – title, author, journal, year	Ofatumumab versus teriflunomide in multiple sclerosis. Hauser SL et al., New Engl J Med 2020;383:546-57 [4]
Study type and design	Randomised, double-blind, double-dummy, parallel-group phase 3 study in which patients with RMS were randomised 1: 1 to subcutaneous ofatumumab or oral teriflunomide for up to 30 months. The study has been completed.
Follow-up time	The median follow-up time in the study was 1.5 years. More than 30% of patients participated in the study for more than 2 years.
Population (inclusion and exclusion criteria)	Inclusion criteria: • 18 to 55 years of age • Diagnosis of MS • Relapsing MS: RRMS or SPMS • At least 1 relapse during the previous 1 year or 2 relapses during the previous 2 years or a positive gadolinium-enhancing MRI scan in previous year • EDSS score of 0 to 5.5 Exclusion criteria: • Primary progressive MS • Disease duration of more than 10 years in patients with an EDSS score of 2 or less • Patients with an active chronic disease of the immune system other than MS • Patients at risk of developing or having reactivation of hepatitis Patients with active systemic infections or with neurological findings consistent with PML
Intervention	A total of 465 patients were randomised to ofatumumab 20 mg s.c., every 4 weeks after an initial loading dose on days 1, 7 and 14
Baseline characteristics	

Characteristic	Ofatumumab (N = 465)	Teriflunomide (N = 462)
Age, years	38.9±8.8	37.8±9.0
Female sex, n (%)	318 (68.4)	317 (68.6)

ASCLEPIOS I			
	Type of MS, n (%) Relapsing–remitting Secondary progressive	 438 (94.2) 27 (5.8)	 434 (93.9) 28 (6.1)
	Time since symptom onset, years	8.36±6.84	8.18±7.21
	Time since diagnosis, years	5.77±6.05	5.64±6.20
	No previous disease-modifying therapy, n (%)	191 (41.1)	182 (39.4)
	Previous disease-modifying therapy, n (%)		
	Any interferon beta	189 (40.6)	193 (41.8)
	Glatiramer acetate	124 (26.7)	106 (22.9)
	Dimethyl fumarate	36 (7.7)	37 (8.0)
	Teriflunomide	8 (1.7)	6 (1.3)
	Daclizumab	5 (1.1)	12 (2.6)
	Fingolimod	10 (2.2)	15 (3.2)
	Natalizumab	31 (6.7)	36 (7.8)
	Any B-cell therapy	2 (0.4)	3 (0.6)
	Laquinimod	5 (1.1)	4 (0.9)
	Other disease-modifying therapy	52 (11.2)	65 (14.1)
	No. of relapses in previous 12 months	1.2±0.6	1.3±0.7
	No. of relapses in previous >12–24 months	0.9±0.9	0.9±1.2
	EDSS score	2.97±1.36	2.94±1.36
	No. of gadolinium-enhancing lesions per T1-weighted MRI scan	1.7±4.9	1.2±2.6
	Absence of gadolinium-enhancing lesions on T1-weighted MRI, n (%)	291 (62.6)	293 (63.4)
	Volume of lesions on T2-weighted MRI, cm^3	13.2±13.3	13.1±14.6
	Neurofilament light chain concentration, pg/mL	13.3±13.2	11.7±9.3
	Normalised brain volume, cm^3	1439±81	1442±79

Primary and secondary endpoints

Primary endpoint

Annualised relapse rate (confirmed relapses)

Time frame: baseline up to 2.5 years

ARR was the number of confirmed relapses in a year, calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of time in study. A confirmed MS relapse was defined as one accompanied by a clinically relevant change in the EDSS performed by the Independent EDSS rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores or 2 points on one functional score (excluding changes involving bowel/bladder or cerebral functional system). Comparisons were made to the previous rating (the last EDSS rating that did not occur during a relapse).

Secondary endpoints

3-month confirmed disability worsening (3mCDW) based on EDSS

Time frame: baseline, every 3 months up to 2.5 years

A 3-month confirmed disability worsening (3mCDW) was defined as an increase from baseline in EDSS score sustained for at least 3 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for

ASCLEPIOS I	

patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively.

6-month confirmed disability worsening (6mCDW) based on EDSS
Time frame: baseline, every 3 months up to 2.5 years

A 6-month confirmed disability worsening (6mCDW) was defined as an increase from baseline in EDSS score sustained for at least 6 months. For patients with a baseline EDSS of 0, the criterion for disability worsening was an increase in EDSS of ≥1.5, for patients with a baseline EDSS of 1 to 5 or ≥5.5, the criterion for disability worsening was an increase in EDSS of ≥1 or ≥0.5, respectively.

6-month confirmed disability improvement (6mCDI) based on EDSS
Time frame: baseline, every 3 months up to 2.5 years

A 6-month confirmed disability improvement is a decrease from baseline in EDSS score sustained for at least 6 months.

Number of Gd-enhancing T1 lesions per MRI scan
Time frame: baseline, yearly up to 2.5 years

Total number of Gd-enhancing T1 lesions across all scans per patient adjusted for different number of scans due to variable follow-up time in study.

Number of new or enlarging T2 Lesions on MRI per year (annualised lesion rate)
time frame: baseline, yearly up to 2.5 years

Number of new/enlarging T2 lesions on last available MRI scan compared to baseline adjusted for different time of scans versus baseline due to variable follow up time in study.

Neurofilament light chain (NfL) concentration in serum
Time frame: month 3, 12 and 24

The NfL concentration (geometric mean concentration) was estimated by treatment and time point with using a repeated measures model on the basis of all evaluable log transformed NfL values.

Annualised rate of brain volume loss based on assessments of percent brain volume change from baseline
Time frame: baseline, months 12 and 24

Percent change from baseline in brain volume loss on all MRI scans adjusted for different time of scan versus baseline due to variable follow up time in study.

Other secondary endpoints (specified in the protocol)

- Time to a 6-month confirmed cognitive impairment (6mCCD) defined as a 4-point deterioration measured by the Symbol Digit Modalities Test (SDMT)
- Time to 6 months of confirmed deterioration of at least 20% on the 25-foot gait test (T25FW)
- Time to 6-month confirmed deterioration of at least 20% in 9-hole peg test (9HPT)
- Proportion of patients without signs of disease activity (NEDA) in years 1 and 2
- Physical and psychological impact of MS disease measured by Multiple Sclerosis Impact Scale (MSIS-29)

ASCLEPIOS I	
	Exploratory endpoints • PRO measured using the EQ-5D • The impact of MS on labour productivity and regular activities assessed by the Work Productivity and Activity Impairment Questionnaire (WPAI: MS)
Method of analysis	Efficacy analyses were intention-to-treat. Data on the ARR were analysed using a negative binomial-regression model, with an offset for time spent in the study in years to adjust for varying treatment durations among patients. The type I error was controlled by a statistical testing procedure, with seven prespecified secondary end points tested; disability worsening confirmed at 3 months or 6 months and disability improvement confirmed at 6 months were tested in pre-planned meta-analyses of the combined studies only if the primary null hypothesis for the ARR was rejected in both the ASCLEPIOS I and II studies independently. Other secondary end points were tested in hierarchical sequential order (number of gadolinium-enhancing lesions per T1-weighted MRI scan, annualised rate of new or enlarging lesions on T2-weighted MRI, serum neurofilament light chain concentration, and annual rate of brain-volume loss) as long as all preceding null hypotheses could be rejected. Data from disability-related endpoints were analysed using a Cox proportional hazards model, model, stratified according to study. Numbers of gadolinium-enhancing lesions on T1-weighted MRI and new or enlarging lesions on T2-weighted MRI were assessed using a negative binomial-regression model. Data on serum neurofilament light chain concentration were analysed using a repeated-measures model after log transformation of the data. The annual rate of brain-volume loss was estimated as the marginal slope estimate from a random-coefficient model with random intercept and slope on the basis of assessments of the percentage change from baseline in brain volume performed at month 12, month 24, and at the end of the study. The primary endpoint and key secondary end points used analysis methods that handle missing data under missing-at-random assumptions.
Subgroup analyses	'Newly diagnosed, treatment-naïve patients' were a predefined subgroup. Additional predefined subgroups are described below. It should be emphasized that the subgroups were not powered to show a difference and that the information below is derived from data on file. • Age (≤40,> 40) • Sex (women, men) • Body weight (<Q1, ≥Q1 and <Q2, ≥Q2 and <Q3, ≥Q3) • Region (Europe, North America, rest of the world) • MS type (RRMS, Active SPMS) • Baseline EDSS (≤3.5,> 3.5) • Number of attacks in the previous 2 years (≤2,> 2) • Gd-charging T1 lesions at baseline (0,> 0) • Volume of T2 lesions at baseline (<Q1, ≥Q1 and <Q2, ≥Q2 and <Q3, ≥Q3)

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ASCLEPIOS I	
	• Previous disease-modifying MS treatment (previously treated, treatment naive) The subgroups were analysed for the following endpoints: • Annual attack rate (in the case of a negative binomial model) • 3-month confirmed disability worsening (by Cox's proportional hazard model) • 6-month confirmed disability worsening (by Cox's proportional hazard model) • 6-month confirmed disability improvement (by Cox's proportional hazard model) • Number of Gadolinium-positive T1 lesions per MRI scan (in a negative binomial model) • Number of new or enlarged T2 lesions on MRI per years (in a negative binomial model) • Annual loss of brain volume (by a random coefficient model) • Neurofilament light chain (NfL) concentration in serum at month 3 (by analysis of variance with repeated measurements)

Abbreviations: ARR, annualised relapse rate; EDSS, Expanded disability status scale; MS, multiple sclerosis; NfL, neurofilament light chain; RRMS, relapsing-remitting MS; s.c., subcutaneously; SPMS, secondary progressive MS

Table 15 Main characteristics for ASCLEPIOS II

ASCLEPIOS II	
Study name	ASCLEPIOS II
NCT numbers	NCT02792231
Objective	To compare the efficacy and safety of ofatumumab administered s.c. every 4 weeks versus teriflunomide administered orally once daily in patients with relapsing multiple sclerosis
Publications – title, author, journal, year	Ofatumumab versus teriflunomide in multiple sclerosis. Hauser SL et al., New Engl J Med 2020;383:546-57 [4]
Study type and design	Randomised, double-blind, double-dummy, parallel-group phase 3 study in which patients with RMS were randomised 1: 1 to subcutaneous ofatumumab or oral teriflunomide for up to 30 months. The study has been completed.
Follow-up time	The median follow-up time in the study was 1.6 years. More than 30% of patients participated in the study for more than 2 years.
Population (inclusion and exclusion criteria)	Inclusion criteria: • 18 to 55 years of age • Diagnosis of MS • Relapsing MS: RRMS or SPMS

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ASCLEPIOS II

- At least 1 relapse during the previous 1 year or 2 relapses during the previous 2 years or a positive gadolinium-enhancing MRI scan in previous year
- EDSS score of 0 to 5.5

Exclusion criteria:

- Primary progressive MS
- Disease duration of more than 10 years in patients with an EDSS score of 2 or less
- Patients with an active chronic disease of the immune system other than MS
- Patients at risk of developing or having reactivation of hepatitis

Patients with active systemic infections or with neurological findings consistent with PML

Intervention

A total of 481 patients were randomised to ofatumumab 20 mg s.c., every 4 weeks after an initial loading dose on days 1, 7 and 14

Baseline characteristics

Characteristic	Ofatumumab (N = 481)	Teriflunomide (N = 474)
Age, years	38.0±9.3	38.2±9.5
Female sex, n (%)	319 (66.3)	319 (67.3)
Type of MS, n (%) Relapsing–remitting Secondary progressive	 452 (94.0) 29 (6.0)	 450 (94.9) 24 (5.1)
Time since symptom onset, years	8.20±7.40	8.19±7.38
Time since diagnosis, years	5.59±6.38	5.48±6.00
No previous disease-modifying therapy, n (%)	195 (40.5)	181 (38.2)
Previous disease-modifying therapy, n (%)		
Any interferon beta	197 (41.0)	193 (40.7)
Glatiramer acetate	118 (24.5)	149 (31.4)
Dimethyl fumarate	36 (7.5)	44 (9.3)
Teriflunomide	13 (2.7)	9 (1.9)
Daclizumab	8 (1.7)	7 (1.5)
Fingolimod	13 (2.7)	10 (2.1)
Natalizumab	26 (5.4)	20 (4.2)
Any B-cell therapy	0	0
Laquinimod	2 (0.4)	7 (1.5)
Other disease-modifying therapy	68 (14.1)	81 (17.1)
No. of relapses in previous 12 months	1.3±0.7	1.3±0.7
No. of relapses in previous >12–24 months	0.7±0.9	0.8±1.0
EDSS score	2.90±1.34	2.86±1.37
No. of gadolinium-enhancing lesions per T1-weighted MRI scan	1.6±4.1	1.5±4.1
Absence of gadolinium-enhancing lesions on T1-weighted MRI, n (%)	270 (56.1)	291 (61.4)
Volume of lesions on T2-weighted MRI, cm^3	14.3±14.2	12.0±13.0

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ASCLEPIOS II			
	Neurofilament light chain concentration, pg/mL	14.7±18.2	13.4±14.0
	Normalised brain volume, cm^3	1441±77	1446±77
Primary and secondary endpoints	See Table 14		
Method of analysis	See Table 14		
Subgroup analyses	See Table 14		

Abbreviations: ARR, annualised relapse rate; EDSS, Expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; s.c., subcutaneously; SPMS, secondary progressive MS.

Table 16 Main study characteristics for OPERA I

OPERA I	
Study name	OPERA I
NCT numbers	NCT01247324
Objective	To evaluate the efficacy and safety of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis
Publications – title, author, journal, year	Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. Hauser et al. N Engl J Med, 376 (3): 221-234, 2017 [12]
Study type and design	Randomised, double-blind, double-dummy, parallel-group phase 3 study in which patients with RMS were randomised 1: 1 to intravenous ocrelizumab at a dose of 600 mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 44 µg three times weekly for 96 weeks. The study is ongoing and expected to be completed in 2023.
Follow-up time	89.3% of patients in the ocrelizumab group and 82.7% in the interferon beta-1a group completed the 96-week treatment period.
Population (inclusion and exclusion criteria)	Inclusion criteria: • 18 to 55 years of age • Diagnosis of MS, in accordance with the revised McDonald criteria (2010) • At least 2 documented clinical attacks within the last 2 years prior to screening or one clinical attack in the years prior to screening (but not within 30 days prior to screening) • Neurologic stability for ≥30 days prior to both screening and baseline • EDSS score 0 to 5.5 inclusive Exclusion criteria: • Primary progressive MS • Disease duration of more than 10 years in patients with an EDSS score of 2 or less at screening

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OPERA I	
	• Contraindications for MRI • Known presence of other neurological disorders which may mimic MS • Pregnancy or lactation • Requirement for chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study • History of or currently active primary or secondary immunodeficiency • History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies • Active infection, or history of or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis) • History of progressive multifocal leukoencephalopathy • Contraindications to or intolerance of oral or i.v. corticosteroids • Contraindications to Rebif or incompatibility with Rebif use
Intervention	A total of 410 patients were randomised to ocrelizumab at a dose of 600 mg by intravenous infusion every 24 weeks, administered as two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter.

Baseline characteristics

Characteristic	Ocrelizumab (N = 410)	IFN Beta-1a (N = 411)
Age, years	37.1±9.3	36.9±9.3
Female sex, n (%)	270 (65.9)	272 (66.2)
Geographic region, n (%)		
US	105 (25.6)	105 (25.5)
Rest of the world	305 (74.4)	306 (74.5)
Time since symptom onset, years	6.74±6.37	6.25±5.98
Time since diagnosis, years	3.82±4.80	3.71±4.63
No previous disease-modifying therapy, n/N (%)	301/408 (73.8)	292/409 (71.4)
Previous disease-modifying therapy, n/N (%)	107/408 (26.2)	117/409 (28.6)
Interferon	81/408 (19.9)	86/409 (21.0)
Glatiramer acetate	38/408 (9.3)	37/409 (9.0)
Dimethyl fumarate	1/408 (0.2)	0/409
Fingolimod	1/408 (0.2)	0/409
Natalizumab	0/408	1/409 (0.2)
Other disease-modifying therapy	2/408 (0.5)	3/409 (0.7)
No. of relapses in previous 12 months	1.31±0.65	1.33±0.64
Mean EDSS score	2.86±1.24	2.75±1.29
No. of gadolinium-enhancing lesions per T1-weighted MRI scan		
0	233/405 (57.5)	252/407 (61.9)
1	64/405 (15.8)	52/407 (12.8)
2	30/405 (7.4)	30/407 (7.4)

OPERA I			
	3 ≥4	20/405 (4.9) 58/405 (14.3)	16/407 (3.9) 57/407 (14.0)
	No. of lesions on T2-weighted MRI	51.04±39.00	51.06±39.90
	Volume of lesions on T2-weighted MRI, cm^3	10.84±13.90	9.74±11.28
	Normalised brain volume, cm^3	1500.93±84.10	1499.18±87.68
Primary and secondary endpoints	**Primary endpoint** ***Annualised relapse rate (confirmed relapses)*** Time frame: week 96 ARR was protocol-defined and calculated as the total number of relapses for all participants in the treatment group divided by the total participant-years of exposure to that treatment. **Secondary endpoints** ***Time to onset of confirmed disability progression (CDP) for at least 12 weeks during the double-blind treatment period*** Time frame: week 108 Disability progression was defined as an increase in the EDSS score of: A)≥1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 B) ≥0.5 point from the baseline EDSS score when the baseline score was >5.5 The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of neurological worsening. EDSS assessment and who were on treatment at time of clinical cut-off date were censored at the date of their last EDSS assessment. ***Number of T1 gadolinium (gd)-enhancing lesions as detected by brain MRI during the double-blind treatment*** Time frame: baseline up to week 96 The total number of T1 gadolinium-enhancing lesions for all participants in the treatment group was calculated as the sum of the individual number of lesions at weeks 24, 48, and 96. ***Number of new, and/or enlarging t2 hyperintense lesions as detected by brain MRI during the double-blind treatment*** Time frame: baseline up to week 96 The total number of new and/or enlarging T2 lesions for all participants in the treatment group was calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96. ***Percentage of participants with confirmed disability improvement (CDI) for at least 12 weeks*** Time frame: week 96 Disability improvement was assessed only for the subgroup of participants with a baseline EDSS score of >= 2.0. It was defined as a reduction in EDSS score of: A) >=1.0 from the baseline EDSS score when the baseline score was >=2 and <=5.5 B) >= 0.5 when the baseline EDSS score > 5.5. The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure		

OPERA I	
	was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. ***Time to onset of confirmed disability progression (CDP) for at least 24 weeks during the double-blind treatment period*** Time Frame: week 108 Disability progression was defined as an increase in the EDSS) score of: A) ≥1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 B) ≥0.5 point from the baseline EDSS score when the baseline score was >5.5 The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). This outcome measure was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening. Participants who had initial disability progression with no confirmatory EDSS assessment and who were on treatment at time of clinical cut-off date were censored at the date of their last EDSS assessment. ***Number of T1 hypointense lesions during the double-blind treatment*** Time Frame: baseline up to week 96 The total number of new T1-hypo-Intense Lesions (Chronic Black Holes) for all participants in the treatment group was calculated as the sum of the individual number of new lesions at Weeks 24, 48, and 96. ***Change from baseline in MS functional composite (MSFC) score to week 96*** Time frame: baseline to week 96 MSFC score consists of: A) Timed 25-Foot walk; B) 9-Hole Peg Test (9-HPT); and C) Paced Auditory Serial Addition Test (PASAT-3 version). The MSFCS is based on the concept that scores for these three dimensions (arm, leg, and cognitive function) are combined to create a single score (the MSFC) that can be used to detect change over time in a group of participants with MS. Since the three primary measures differ in what they actually measure, a common composite score for the three different measures i.e., Z- score was selected for the purpose. MSFC Score = (Z arm, average + Z leg, average + Z cognitive) / 3.0. The results from each of these three tests are transformed into Z-scores and averaged to yield a composite score for each participant at each time point. A score of +1 indicates that, on average, an individual scored 1 SD better than the reference population and a score of -1 indicates that an individual scored 1 SD worse than the reference population. ***Percent change in brain volume as detected by brain MRI from week 24 to week 96*** Time frame: from week 24 up to week 96 Brain volume was recorded as an absolute 'normalised' value at the baseline visit then recorded at subsequent visits as a percentage change relative to the absolute value at the baseline visit. Therefore, brain volume at week 24 was calculated as the brain volume at the baseline visit multiplied by 1 + ([percentage change in brain volume from baseline visit to Week 24]/100). ***Change from baseline in short form health survey-36 (SF-36) physical component summary score at week 96*** Time frame: baseline to week 96 The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores (domains) as well as

OPERA I	
	psychometrically based physical and mental health summary measures. The SF-36 taps 8 health concepts: physical functioning, bodily pain, physical role functioning, emotional role functioning, emotional well-being, social functioning, vitality, and general health perceptions. The 8 scales are further summarized to 2 distinct higher-ordered clusters: the physical composite score (PCS) and mental composite t-score (MCS). The range for all 8 domains as well as for the composite t- scores is from 0 to 100 with 100 as best possible health status and 0 as worst health status. ***Percentage of participants who have no evidence of disease activity (NEDA) up to week 96*** Time frame: week 96 NEDA was defined only for participants with a baseline EDSS score >=2.0. The EDSS scale ranges from 0 (normal neurological exam) to 10 (death due to multiple sclerosis). Participants who completed the 96- week treatment period were considered as having evidence of disease activity if at least one protocol- defined relapse (PDR), a confirmed disability progression (CDP) event or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions) was reported during the 96-week treatment period, otherwise the participant was considered as having NEDA. ***Number of participants with adverse events*** Time frame: baseline up to week 96 AEs included infusion related reactions (IRRs) and serious MS relapses, but excluded non-serious MS relapses. Serious adverse events included serious MS relapses and serious IRRs. Exposure to ocrelizumab (area under the concentration - time curve, AUC) Time frame: pre-infusion at weeks 1, 24, 48, 72; and 30 minutes post-infusion at week 72; at any time during weeks 84 and 96 AUC represents total drug exposure for one dosing interval after the 4th dose. ***Number of participants with anti-drug antibodies (ADAs) to ocrelizumab*** Time frame: baseline up to week 96 Number of participants positive for ADAs to ocrelizumab was the number of post-baseline evaluable participants determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Method of analysis	Efficacy analyses were intention-to-treat. The ARR was analysed using a negative binomial model testing for treatment differences between ocrelizumab and interferon beta-1a, with adjustment according to geographic region and baseline EDSS score. Ten 10 secondary efficacy endpoints were prespecified to be tested in a hierarchical order at a two-sided alpha of 0.05. Seven endpoints of this hierarchy were to be tested in each individual study (OPERA I and II), and 3 endpoints (disability progression confirmed at 12 weeks and at 24 weeks and disability improvement confirmed at 12 weeks) were to be assessed in the pooled data set for the two studies. For the percent change in brain volume, estimates were from analysis based on a mixed-effect model of repeated measures using an unstructured covariance matrix.
Subgroup analyses	None.

Abbreviations: ADA, anti-drug antibodies; ARR, annualised relapse rate; AUC: area under curve; EDSS, Expanded disability status scale; SD, standard deviation.

Table 17 Main study characteristics for OPERA II

OPERA II	
Study name	OPERA II
NCT numbers	NCT01412333
Objective	To evaluate the efficacy and safety of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis
Publications – title, author, journal, year	Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. Hauser et al. N Engl J Med, 376 (3): 221-234, 2017 [12]
Study type and design	Randomised, double-blind, double-dummy, parallel-group phase 3 study in which patients with RMS were randomised 1: 1 to receive either ocrelizumab 600 mg or matching placebo intravenously as 300 mg infusions on days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent infusions every 24 weeks, with placebo injections matching interferon beta-1a subcutaneously 3 times per week; or interferon beta-1a 44 mcg subcutaneous injections 3 times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks). The study is ongoing and expected to be completed in 2023.
Follow-up time	86.3% of patients in the ocrelizumab group and 76.6% in the interferon beta-1a group completed the 96-week treatment period.
Population (inclusion and exclusion criteria)	Inclusion criteria: • 18 to 55 years of age • Diagnosis of MS, in accordance with the revised McDonald criteria (2010) • At least 2 documented clinical attacks within the last 2 years prior to screening or one clinical attack in the years prior to screening (but not within 30 days prior to screening) • Neurologic stability for ≥30 days prior to both screening and baseline • EDSS score 0 to 5.5 inclusive Exclusion criteria: • Primary progressive MS • Disease duration of more than 10 years in patients with an EDSS score of 2 or less at screening • Contraindications for MRI • Known presence of other neurological disorders which may mimic MS • Pregnancy or lactation • Requirement for chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study • History of or currently active primary or secondary immunodeficiency

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OPERA II

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Active infection, or history of or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis)
- History of progressive multifocal leukoencephalopathy
- Contraindications to or intolerance of oral or i.v. corticosteroids
- Contraindications to Rebif or incompatibility with Rebif use

Intervention

A total of 417 patients were randomised to ocrelizumab at a dose of 600 mg by intravenous infusion every 24 weeks, administered as two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter.

Baseline characteristics

Characteristic	Ocrelizumab (N = 417)	IFN Beta-1a (N = 418)
Age, years	37.2±9.1	37.4±9.0
Female sex, n (%)	271 (65.0)	280 (67.0)
Geographic region, n (%)		
US	112 (26.9)	114 (27.3)
Rest of the world	305 (73.1)	304 (72.7)
Time since symptom onset, years	6.72±6.10	6.68±6.13
Time since diagnosis, years	4.15±4.95	4.13±5.07
No previous disease-modifying therapy, n/N (%)	304/417 (72.9)	314/417 (75.3)
Previous disease-modifying therapy, n/N (%)	113/417 (27.1)	103/417 (24.7)
Interferon	80/417 (19.2)	75/417 (18.0)
Glatiramer acetate	39/417 (9.4)	44/417 (10.6)
Dimethyl fumarate	0/417	0/417
Fingolimod	4/417 (1.0)	0/417
Natalizumab	1/417 (0.2)	0/417
Other disease-modifying therapy	1/417 (0.2)	1/417 (0.2)
No. of relapses in previous 12 months	1.32±0.69	1.34±0.73
Mean EDSS score	2.78±1.30	2.84±1.38
No. of gadolinium-enhancing lesions per T1-weighted MRI scan		
0	252/413 (61.0)	243/415 (58.6)
1	58/413 (14.0)	62/415 (14.9)
2	33/413 (8.0)	38/415 (9.2)
3	15/413 (3.6)	14/415 (3.4)
≥4	55/413 (13.3)	58/415 (14.0)
No. of lesions on T2-weighted MRI	49.26±38.59	51.01±35.69
Volume of lesions on T2-weighted MRI, cm^3	10.73±14.28	10.61±12.30
Normalised brain volume, cm^3	1503.90±92.63	1501.12±90.98

Primary and secondary endpoints

See Table 16

Method of analysis

See Table 16

OPERA II	
Subgroup analyses	None.

Abbreviations: ARR, annualised relapse rate; EDSS, Expanded disability status scale; SD, standard deviation.

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7.3 Results per study

Table 18 Results of ASCLEPIOS I

Study name:	ASCLEPIOS I: A Randomized, Double-blind, Double-dummy, Parallel-group Study Comparing the Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis										
NCT number:	NCT02792218										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
CDP-3, % of patients	Ofatumumab (20 mg q4w)	465	11.3	-4.1		NA	0.650	0.45;0.96	0.026	See statistical considerations, appendix 7.6	Table 2, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	459	15.4								
SAE, % of patients	Ofatumumab (20 mg q4w)	465	10.3	2.10	-1.67;5.84	0.2724	1.255	0.837;1.883	NA	See statistical considerations, appendix 7.6	Table 3, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	462	8.2								

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Study name:	ASCLEPIOS I: A Randomized, Double-blind, Double-dummy, Parallel-group Study Comparing the Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis
NCT number:	NCT02792218

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Annualised relapse rate	Ofatumumab (20 mg q4w)	465	0.11 (0.09; 0.14)	-0.11	-0.16; -0.06	<0.0001	0.49	0.37; 0.65	<0.001	See statistical considerations, appendix 7.6	Table 2, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	462	0.22 (0.18; 0.26)								
SDMT, % of patients avoiding a worsening of 4 points	Ofatumumab (20 mg q4w)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file
	Teriflunomide (14 mg daily)	[redacted]	[redacted]								

Study name:	ASCLEPIOS I: A Randomized, Double-blind, Double-dummy, Parallel-group Study Comparing the Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis
NCT number:	NCT02792218

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
EQ-5D utility score, mean change, week 96	Ofatumumab (20 mg q4w)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file
	Teriflunomide (14 mg daily)	[redacted]	[redacted]								
EQ-5D VAS score, mean change, week 96	Ofatumumab (20 mg q4w)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file
	Teriflunomide (14 mg daily)	[redacted]	[redacted]								

p-values for CDP-3: The column with values for absolute differences has no p-values because it is 'artificial'. The p-value in the column with relative differences refer to the Hazard-Ratio as mentioned in the reference and is calculated from the CI.

p-values for annualised rates: the p-values mentioned for absolute differences are calculated whereas the p-values mentioned for relative differences are from the reference.

p-values for other outcomes are mentioned for absolute differences and are calculated values.

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; EQ-5D, EuroQol Group 5-dimension health-related quality of life instrument; N, number of subjects; NA, not applicable; NCT, national clinical trial; q4w, every 4 weeks; SAE, serious adverse event; SDMT, symbol digit modalities test; VAS, visual analogue scale. Grey fields mark calculated values.

Table 19 Results of ASCLEPIOS II

Study name:	**ASCLEPIOS II: A Randomized, Double-blind, Double-dummy, Parallel-group Study Comparing the Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis.**
NCT number:	**NCT02792231**

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CDP-3, % of patients	Ofatumumab (20 mg q4w)	479	10.5	-4.1		NA	0.66	0.45;0.97	0.034	See statistical considerations, appendix 7.6	Table 2, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	472	14.6								
SAE, % of patients	Ofatumumab (20 mg q4w)	481	7.9	0.31	-3.12;3.72	0.8600	1.040	0.671;1.612	NA	See statistical considerations, appendix 7.6	Table 3, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	474	7.6								
Annualised relapse rate	Ofatumumab (20 mg q4w)	481	0.10 (0.08; 0.13)	-0.15	-0.2; -0.09	<0.0001	0.42	0.31; 0.56	<0.001	See statistical considerations, appendix 7.6	Table 2, Hauser 2020 [4]
	Teriflunomide (14 mg daily)	474	0.25 (0.21; 0.3)								

Study name:	ASCLEPIOS II: A Randomized, Double-blind, Double-dummy, Parallel-group Study Comparing the Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis.										
NCT number:	NCT02792231										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SDMT, % of patients avoiding a worsening of 4 points	Ofatumumab (20 mg q4w) Teriflunomide (14 mg daily)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file
EQ-5D utility score, mean change, week 96	Ofatumumab (20 mg q4w) Teriflunomide (14 mg daily)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file
EQ-5D VAS score, mean change, week 96	Ofatumumab (20 mg q4w) Teriflunomide (14 mg daily)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6	Novartis, data on file

p-values for CDP-3: The column with values for absolute differences has no p-values because it is 'artificial'. The p-value in the column with relative differences refer to the Hazard-Ratio as mentioned in the reference and is calculated from the CI.

p-values for annualised rates: the p-values mentioned for absolute differences are calculated whereas the p-values mentioned for relative differences are from the reference.

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p-values for other outcomes are mentioned for absolute differences and are calculated values.

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; EQ-5D, EuroQol Group 5-dimension health-related quality of life instrument; N, number of subjects; NA, not applicable; NCT, national clinical trial; q4w, every 4 weeks; SAE, serious adverse event; SDMT, symbol digit modalities test; VAS, visual analogue scale.

Grey fields mark calculated values.

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Table 20 Results of OPERA I

Study name:	**OPERA I: A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif®) in Patients with Relapsing Multiple Sclerosis**										
NCT number:	**NCT01247324**										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CDP-3*, % of patients	Ocrelizumab (600 mg q24w)	410	7.6	-5.05	-7.50;-1.15	NA	0.570	0.37;0.90	0.013	See statistical considerations, appendix 7.6	Table 2, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	411	12.2								
SAE, % of patients	Ocrelizumab (600 mg q24w)	408	6.9	-0.96	-4.57;2.66	0.5988	0.877	0.538;1.429	NA	See statistical considerations, appendix 7.6	Table 3, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	409	7.8								
Annualised relapse rate	Ocrelizumab (600 mg q24w)	410	0.16 (0.12; 0.20)	-0.14	-0.193; -0.079	<0.0001	0.54	0.40; 0.72	<0.0001		Table 2, Hauser 2017 [12]

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Study name:	OPERA I: A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif®) in Patients with Relapsing Multiple Sclerosis										
NCT number:	NCT01247324										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Interferon Beta-1a (44 µg 3 times weekly)	411	0.29 (0.24; 0.36)							See statistical considerations, appendix 7.6	
SF-36 physical-component summary score, mean change from baseline to week 96	Ocrelizumab (600 mg q24w)	410	0.04 (-0.86; 0.93)	0.69	-0.41; 1.80	0.2853	NA	NA	NA	See statistical considerations, appendix 7.6	Table 2, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	411	-0.65 (-1.59; 0.28)								

p-values for CDP-3: The column with values for absolute differences has no p-values because it is 'artificial'. The p-value in the column with relative differences refer to the Hazard-Ratio as mentioned in the reference and is calculated from the CI.

p-values for annualised rates: the p-values mentioned for absolute differences are calculated whereas the p-values mentioned for relative differences are from the reference.

p-values for other outcomes are mentioned for absolute differences and are calculated values.

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; N, number of subjects; NA, not applicable; NCT, national clinical trial; q24w, every 24 weeks; SAE, serious adverse event; SF-36, 36-Item Short Form Survey.

*Measured after 12 weeks.

Grey fields mark calculated values.

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Table 21 Results of OPERA II

Study name:	OPERA II: A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif) in Patients with Relapsing Multiple Sclerosis										
NCT number:	NCT01412333										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CDP-3*, % of patients	Ocrelizumab (600 mg q24w)	417	10.6	-5.3	-8.46;-1.12	NA	0.63	0.42;0.92	0.021	See statistical considerations, appendix 7.6	Table 2, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	418	15.1								
SAE, % of patients	Ocrelizumab (600 mg q24w)	417	7.0	-2.64	-6.39;1.14	0.1691	0.725	0.458;1.147	NA	See statistical considerations, appendix 7.6	Table 3, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	417	9.6								
Annualised relapse rate	Ocrelizumab (600 mg q24w)	417	0.16 (0.12; 0.20)	-0.13	-0.192; -0.078	<0.0001	0.53	0.40; 0.71	<0.0001	See statistical considerations, appendix 7.6	Table 2, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	418	0.29 (0.23; 0.36)								

Study name:	OPERA II: A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif) in Patients with Relapsing Multiple Sclerosis										
NCT number:	NCT01412333										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SF-36 physical-component summary score, mean change from baseline to week 96	Ocrelizumab (600 mg q24w)	417	0.33 (-0.55; 1.20)	1.16	0.05; 2.27	0.0662	NA	NA	NA	See statistical considerations, appendix 7.6	Table 2, Hauser 2017 [12]
	Interferon Beta-1a (44 µg 3 times weekly)	418	-0.83 (-1.76; 0.09)								

p-values for CDP-3: The column with values for absolute differences has no p-values because it is 'artificial'. The p-value in the column with relative differences refer to the Hazard-Ratio as mentioned in the reference and is calculated from the CI.

p-values for annualised rates: the p-values mentioned for absolute differences are calculated whereas the p-values mentioned for relative differences are from the reference.

p-values for other outcomes are mentioned for absolute differences and are calculated values.

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; N, number of subjects; NA, not applicable; NCT, national clinical trial; q24w, every 24 weeks; SAE, serious adverse event; SF-36, 36-Item Short Form Survey.

*Measured after 12 weeks.

Grey fields mark calculated values.

7.4 Results per PICO

Table 22 Results referring to clinical question 1: ofatumumab versus teriflunomide.

Results per outcome:	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Difference	CI	*P* value	
CDP-3, % of patients	ASCLEPIOS I and ASCLEPIOS II	-4.90	-7.20 ; -1.98	NA	0.655	0.500;0.858	0.0021	See statistical considerations, appendix 7.6
SAE, % of patients	ASCLEPIOS I and ASCLEPIOS II	1.116	-1.394;3.625	NA	1.151	0.855;1.550	0.355	See statistical considerations, appendix 7.6
Annualised relapse rate	ASCLEPIOS I and ASCLEPIOS II	-0.128	-0.163;-0.093	<0.0001	NA	NA	NA	See statistical considerations, appendix 7.6
SDMT, % of patients avoiding a worsening of 4 points	ASCLEPIOS I and ASCLEPIOS II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6
EQ-5D utility score, mean change, week 96	ASCLEPIOS I and ASCLEPIOS II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6
EQ-5D VAS score, mean change, week 96	ASCLEPIOS I and ASCLEPIOS II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	See statistical considerations, appendix 7.6

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; EQ-5D, EuroQol Group 5-dimension health-related quality of life instrument; NA, not applicable; SAE, serious adverse event; SDMT, symbol digit modalities test; VAS, visual analogue scale.

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Table 23 Results referring to clinical question 2: ocrelizumab versus interferon beta-1a.

Results per outcome:	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Difference	CI	*P* value	
CDP-3, % of patients	OPERA I and OPERA II	NA	NA	NA	0.603	0.449;0.809	0.0007	See statistical considerations, appendix 7.6
SAE, % of patients	OPERA I and OPERA II	-1,763	-4.346;0.820	NA	0.793	0.567;1.107	0.173	See statistical considerations, appendix 7.6
Annualised relapse rate	OPERA I and OPERA II	-0.136	-0.188;-0.083	<0.0001	NA	NA	NA	See statistical considerations, appendix 7.6
SF-36 physical-component summary score, mean change from baseline to week 96	OPERA I and OPERA II	0.929	0.021;1.837	0.0449	NA	NA	NA	See statistical considerations, appendix 7.6

CDP-3, confirmed disability progression after 3 months; CI, confidence interval; NA, not applicable; SAE, serious adverse event; SF-36, 36-Item Short Form Survey.

*Measured after 12 weeks.

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7.5 Safety information for teriflunomide, ofatumumab and ocrelizumab

Table 24 Safety information for teriflunomide, ofatumumab and ocrelizumab from the SmPCs [3, 9, 11]

	Aubagio® (teriflunomide)	Kesimpta® (ofatumumab)	Ocrevus® (ocrelizumab)
Mechanism of action	Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of T-lymphocytes	Ofatumumab is a fully human anti-CD20 monoclonal immunoglobulin G1 (IgG1) antibody. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells. The binding of ofatumumab to CD20 induces lysis of CD20+ B cells primarily through complement-dependent cytotoxicity (CDC) and, to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.	Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS is not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The capacity of B-cell reconstitution and preexisting humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Posology and method of administration	The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. The recommended dose of teriflunomide is 14 mg once daily.	Treatment should be initiated by a physician experienced in the management of neurological conditions. The recommended dose is 20 mg ofatumumab administered by subcutaneous injection with: • initial dosing at weeks 0, 1 and 2, followed by • subsequent monthly dosing, starting at week 4.	Ocrevus treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs) The following two premedications must be administered prior to each Ocrevus infusion to reduce the frequency and severity of IRRs • 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion • antihistamine approximately 30-60 minutes prior to each Ocrevus infusion • In addition, premedication with an antipyretic (e.g paracetamol) may also be considered approximately 30-60 minutes prior to each Ocrevus infusion. <u>Initial Dose</u> The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion.

			<u>Subsequent Doses</u> Subsequent doses of Ocrevus thereafter are administered as a single 600 mg intravenous infusion every 6 months. The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose. Each infusion should be given over approximately 2 to 3.5 hours (further details in the SmPC)
Contraindications	• Hypersensitivity to the active substance or to any of the excipients • Patients with severe hepatic impairment (Child-Pugh class C) • Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l. Pregnancy must be excluded before start of treatment • Breast-feeding women • Patients with severe immunodeficiency states, e.g. acquired immunodeficiency syndrome (AIDS) • Patients with significantly impaired bone marrow function or significant	• Hypersensitivity to the active substance or to any of the excipients • **Severe active infection until resolution** • Patients in a severely immunocompromised state • Known active malignancy	• Hypersensitivity to the active substance or to any of the excipients • **Current active infection** • Patients in a severely immunocompromised state • Known active malignancies

	anaemia, leucopoenia, neutropenia or thrombocytopenia • Patients with severe active infection until resolution • Patients with severe renal impairment undergoing dialysis • Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome		
Special warnings and precautions for use (more information for each topic is available in the SmPC)	Monitoring • Blood pressure, liver enzymes should be monitored before and during treatment Hepatic effects Hypoproteinaemia Blood Pressure Infections Respiratory reactions Haematological effects Skin reactions • Stevens-Johnson syndrome (SJS) • toxic epidermal necrolysis (TEN) • drug reaction with eosinophilia and systemic symptoms DRESS) Peripheral neuropathy Vaccination Immunosuppressive or immunomodulating therapies Lactose Interference with determination of ionised calcium levels	Traceability Injection-related reactions Infections • Progressive multifocal leukoencephalopathy (PML) (seen with ofatumumab at substantially higher doses in oncology indications) • Hepatitis B reactivation Treatment of severely immunocompromised patients Vaccinations • median time for B-cell repletion was **24.6 weeks**	Traceability Infusion-Related Reactions Hypersensitivity Reactions Infection • Progressive multifocal leukoencephalopathy (PML) • Hepatitis B reactivation • Late neutropenia Malignancies Treatment of severely immunocompromised patients Vaccinations • median time for B-cell repletion was **72.0 weeks**

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Interaction with other medicinal products and other forms of interaction	Potent cytochrome P450 (CYP) and transporter inducers Cholestyramine or activated charcoal CYP2C8 substrate: repaglinide Oral contraceptives CYP1A2 substrate: caffeine Warfarin Organic anion transporter 3 (OAT3) substrates BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3)	Vaccinations Other immunosuppressive or immune-modulating therapies	Vaccinations Immunosuppressants
Fertility, pregnancy and lactation	Teriflunomide may cause serious birth defects when administered during pregnancy. Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. For women receiving teriflunomide treatment, who wish to become pregnant, the medicinal product **should be stopped**, and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l Teriflunomide is **contraindicated** in pregnancy.	Women of childbearing potential should use effective contraception while receiving Kesimpta and for **6 months** after the last administration of Kesimpta. Treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the **first few days after birth**, which is decreasing to low concentrations soon afterwards.	Women of childbearing potential should use contraception while receiving Ocrevus and for **12 months** after the last infusion of Ocrevus Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Women should be **advised to discontinue** breast-feeding during Ocrevus therapy

	Teriflunomide is **contraindicated** during breast-feeding.	Consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, **ofatumumab could be used during breast-feeding if clinically needed**. However, if the patient was treated with ofatumumab up to the last few months of pregnancy, breast-feeding can be started immediately after birth.	
Undesirable effects:	The most commonly reported adverse reactions in the teriflunomide treated patients were: headache, diarrhoea, increased ALT, nausea, and alopecia. In general, headache, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.	The most important and frequently reported adverse reactions are upper respiratory tract infections (39.4%), systemic injection-related reactions (20.6%), injection-site reactions (10.9%) and urinary tract infections (11.9%).	The most important and frequently reported adverse drug reactions (ADRs) were infusion related reactions and infections.
Very common (≥ 1/10)	Headache Diarrhoea, nausea Alanine aminotransferase (ALT) increase Alopecia	Upper respiratory tract infections Urinary tract infections Injection-site reactions (local) Injection-related reactions (systemic)	Upper respiratory tract infection, nasopharyngitis, influenza Blood immunoglobulin M decreased Infusion-related reactions
Common (≥ 1/100 to < 1/10)	Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis	Oral herpes Blood immunoglobulin M decreased	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis Cough, catarrh

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Neutropenia, anaemia Mild allergic reactions Anxiety Paraesthesia, sciatica, carpal tunnel syndrome Palpitations Hypertension Abdominal pain upper, vomiting, toothache Gamma-glutamyltransferase (GGT) increase, aspartate aminotransferase increase Rash, acne Musculoskeletal pain, myalgia, arthralgia Pollakiuria Menorrhagia Pain, asthenia Weight decrease, neutrophil count decrease, white blood cell count decrease, blood creatine phosphokinase increased		Blood immunoglobulin G decreased Neutropenia

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Uncommon (≥ 1/1,000 to < 1/100)	Nail disorders, severe skin reactions Post-traumatic pain		
Not known (cannot be estimated from the available data).	Dyslipidaemia Psoriasis (including pustular)		Late onset of neutropenia

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7.6 Statistical methods

7.6.1 Statistical methods

The endpoints considered were of 3 types:

- binary proportions
- continuous outcomes (QoL, Utility)
- rates (annualised)

There were four treatment arms involved (ofatumumab, teriflunomide, ocrelizumab, interferon beta-1a).

Direct comparison was only possible in two CTRs for ofatumumab versus teriflunomide.

For a given endpoint in the relevant selection of studies, the following steps were performed:

1) a meta-analysis of ofatumumab versus teriflunomide in two studies
2) a meta-analysis of ocrelizumab versus interferon beta-1a in two studies

The meta-analyses of proportions were performed on the log-transformed scale - and then transformed back in order to present estimates and confidence intervals as ratios.
In every case, the meta analysis was conducted as a simple weighted average of the two study specific estimates using inverse squared standard errors as weights. This corresponds to a standard fixed effects meta analysis. The admissibility of doing the meta analysis was checked by the standard Cochran test and calculation of the I2 index.

In general, some simple pre-processing imputation was done on published data in cases where no doubt existed as to the relevant procedure: missing standard errors were derived from reported standard deviations and the number of patients, and missing proportions (and 95% CI') were derived from the number of events and patients. For fractions, a missing risk-ratio could then be derived in almost every case, including a confidence interval.

For the within-study analyses of proportions, the incidences and 95% confidence intervals were found as exact Clopper-Pearson intervals, whereas risk differences, with one exception, were derived directly as Newcombe intervals, since the general principle of finding the absolute difference as $(RR - 1)*P_0$ where RR is the risk/effect ratio and P_0 is the normal comparator level in Danish setting for the given endpoint, could not be used in the present setup. It has not been possible for the applicant to establish the P_0 values.

For the time-to-event outcome CDP-3 the corresponding (adjusted) hazard ratios (HR) from proportional hazards regression were reported, including confidence intervals.

Literature-based Kaplan-Meier (KM) plots of the event/survival experience in the intervention and comparator arms were available and a software-aided imaging technique was employed to derive approximative values for the event-rates over time.

The absolute difference was calculated in two different ways:

A)

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Based on the event-free rate at 24 months in the comparator arm, S_0, an estimate of the difference (intervention<-> comparator) in event-free rate was derived as:

Difference in event-free rate at 24 months $= S_0^{HR} - S_0$

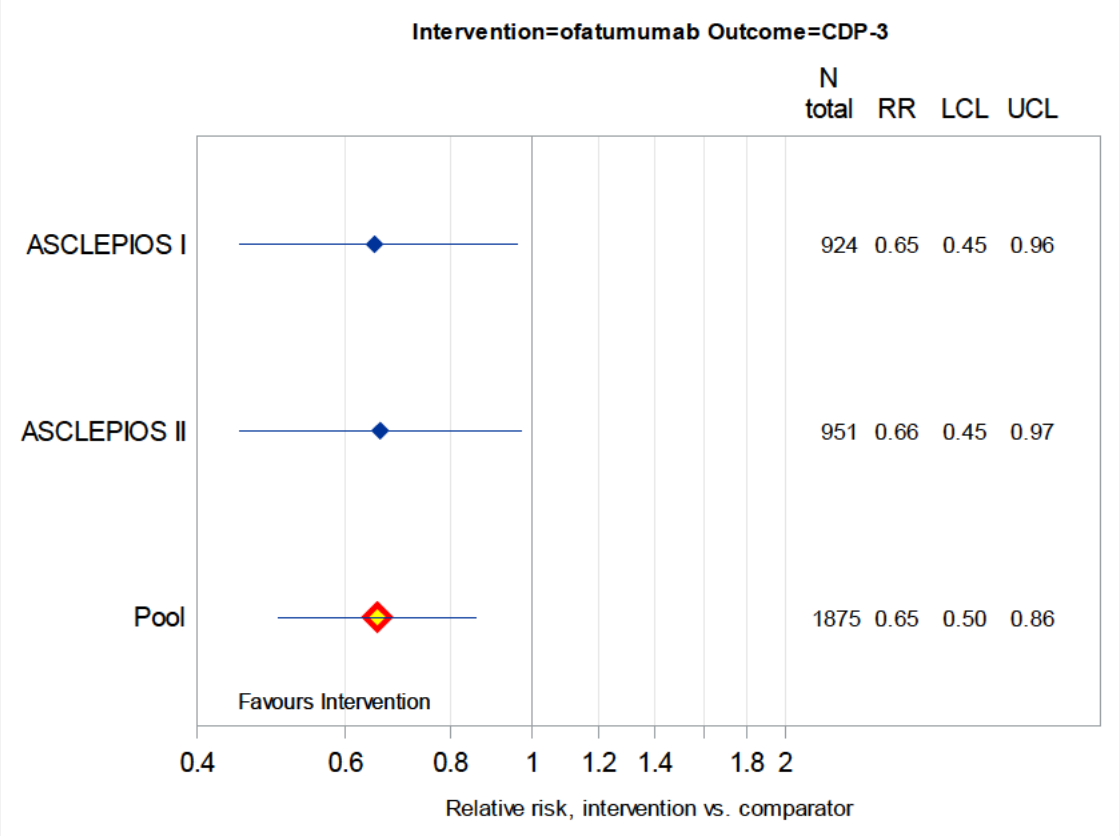
Corresponding limits for the difference were obtained using the same expression with the LL95 and UL95 applied instead of the HR. This approach was used for the meta analysis of the ASCLEPIOS studies.

B)
The simple difference between Kaplan-Meier estimates was derived.
In this case, the simple difference between in24 month KM plots was presented, but without any evaluation of the precision of the estimates (not available from the literature).

7.6.2 Forest plots

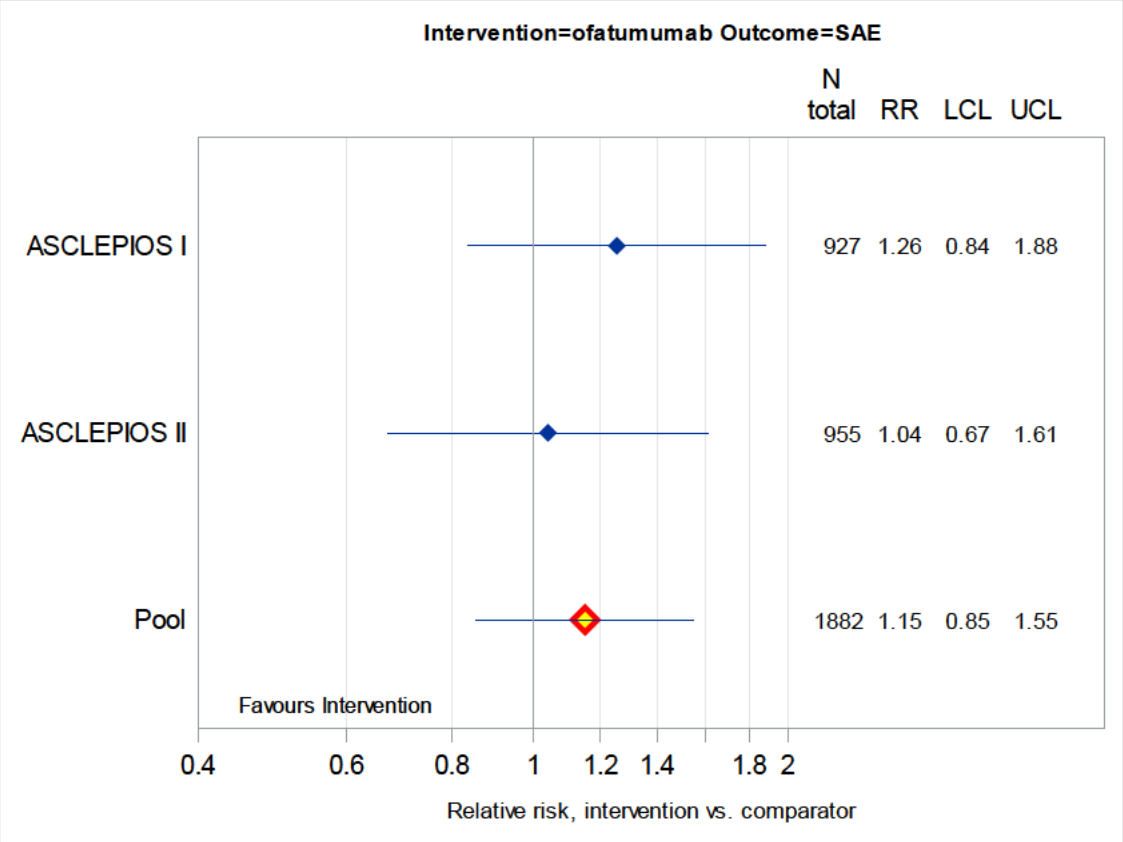
Forest plots for ASCLEPIOS I and II

Figure 2 Forest plot for ofatumumab, CDP-3



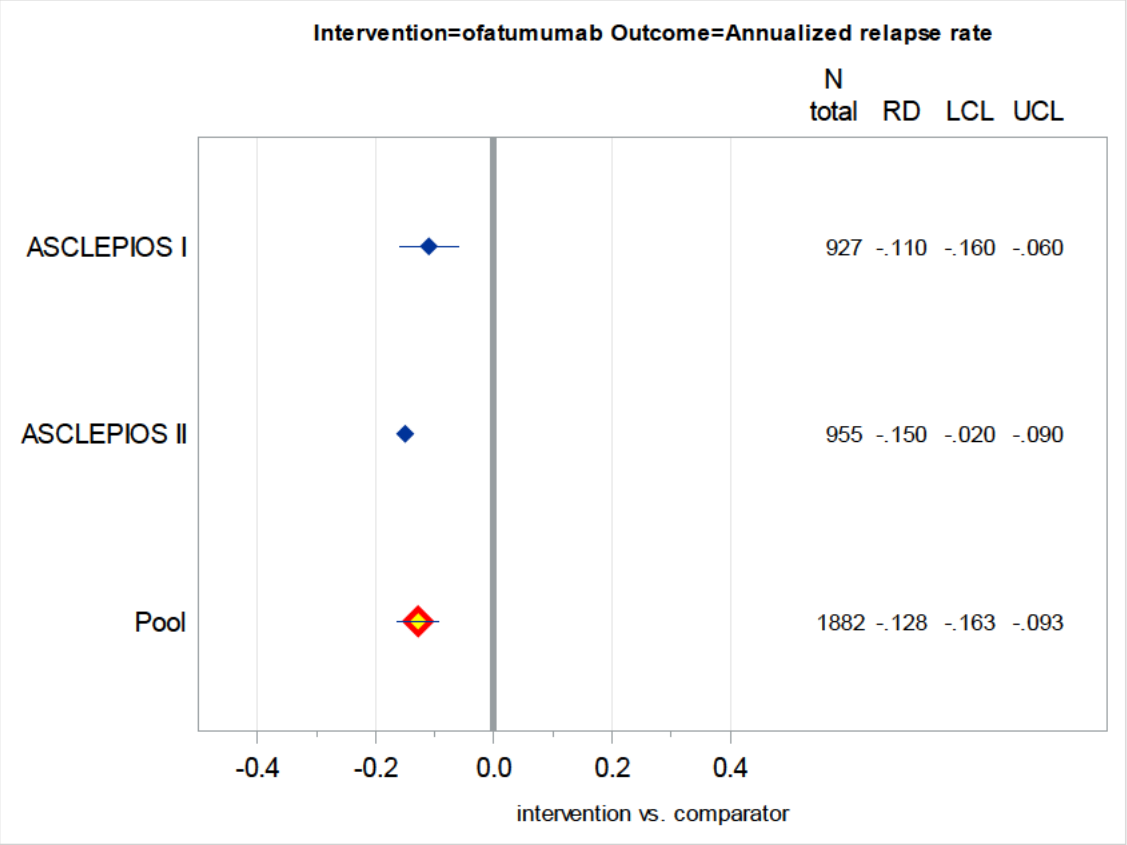
CDP-3, Confirmed disability progression after 3 months; LCL, lower confidence limit; N, number of subjects; RR, relative risk; UCL, upper confidence limit

Figure 3 Forest plot for ofatumumab, SAE



LCL, lower confidence limit; N, number of subjects; RR, relative risk; SAE, serious adverse event; UCL, upper confidence limit

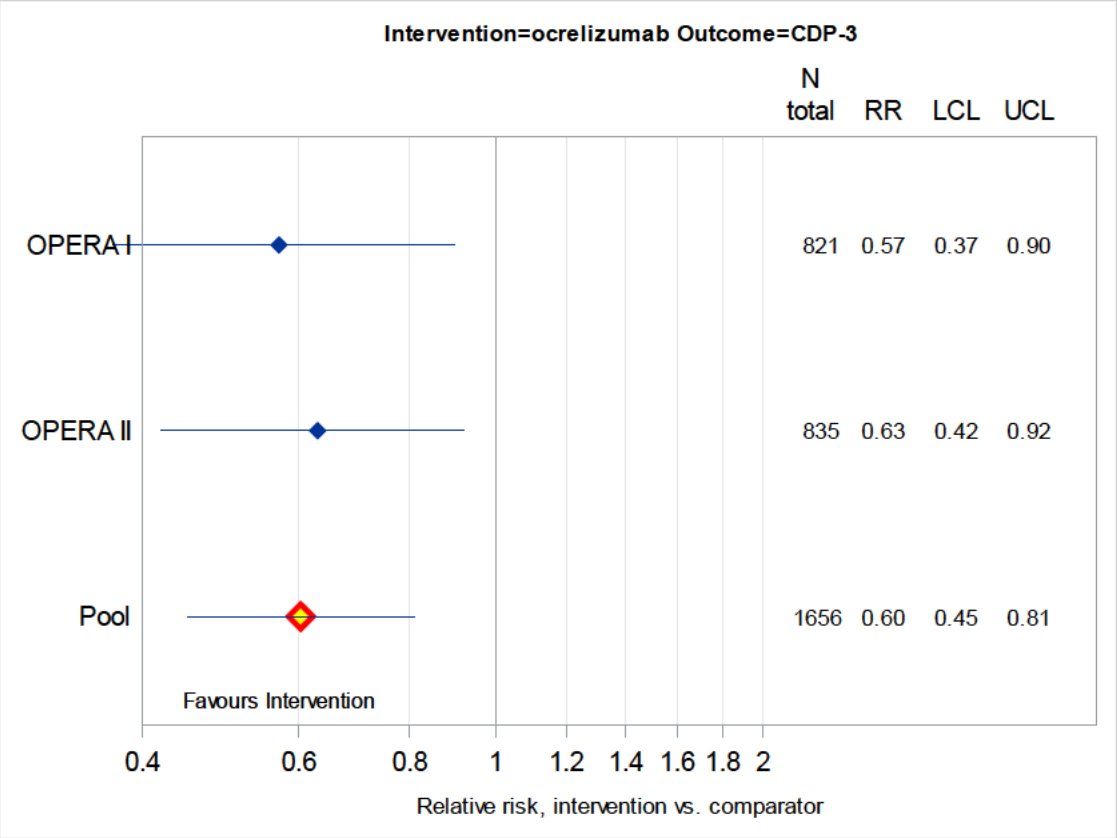
Figure 4 Forest plot for ofatumumab, Annualised relapse rate



LCL, lower confidence limit; N, number of subjects; RD, relative difference; UCL, upper confidence limit

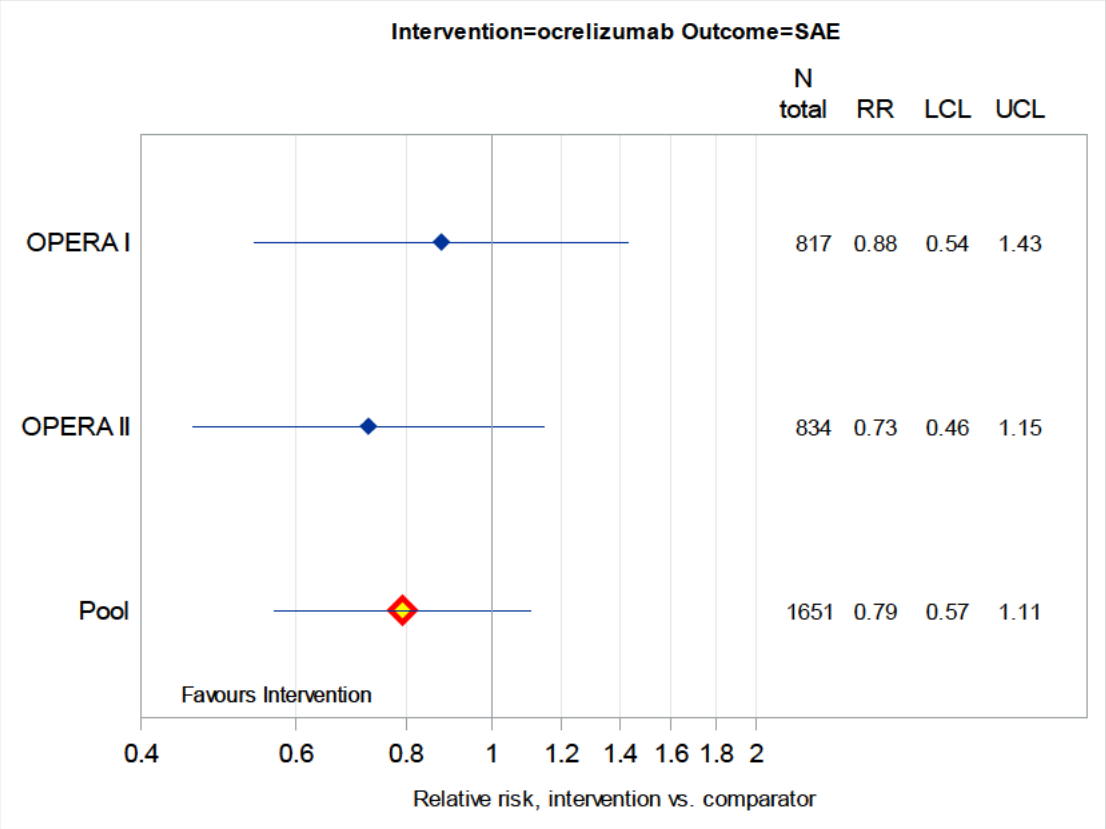
Forest plots for OPERA I and II

Figure 8 Forest plot ocrelizumab, CDP-3



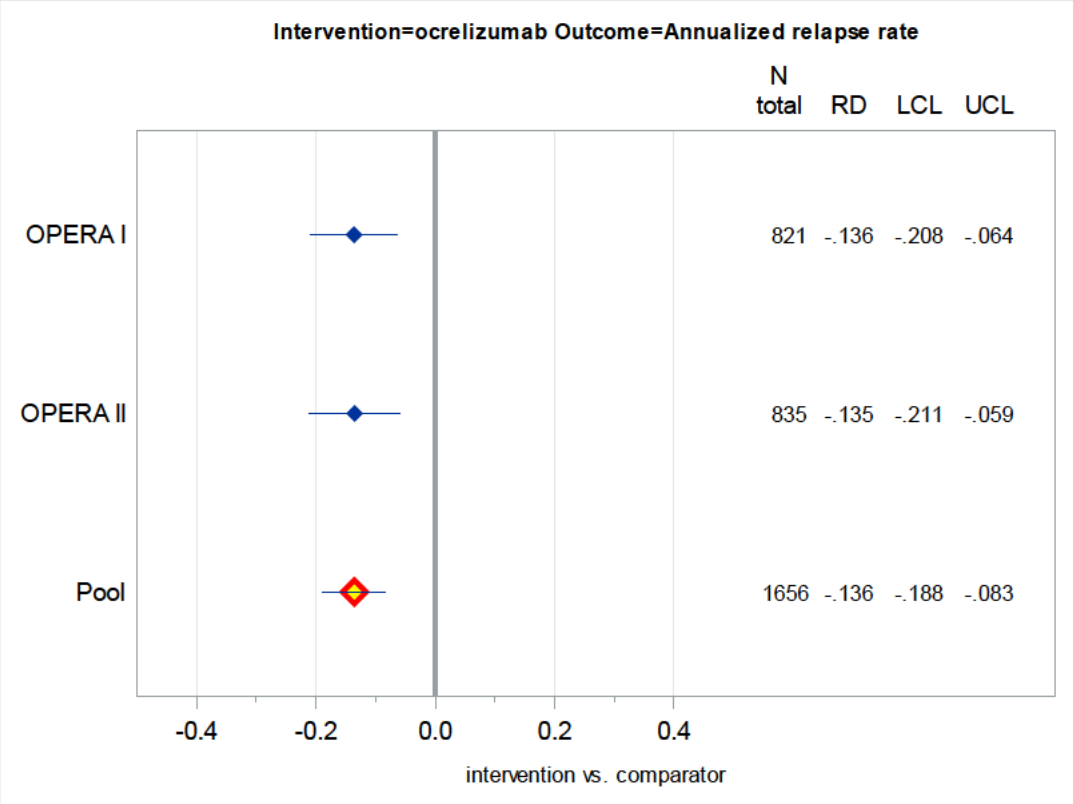
CDP-3, Confirmed disability progression after 3 months; LCL, lower confidence limit; N, number of subjects; RR, relative risk; UCL, upper confidence limit

Figure 9 Forest plot ocrelizumab, SAE



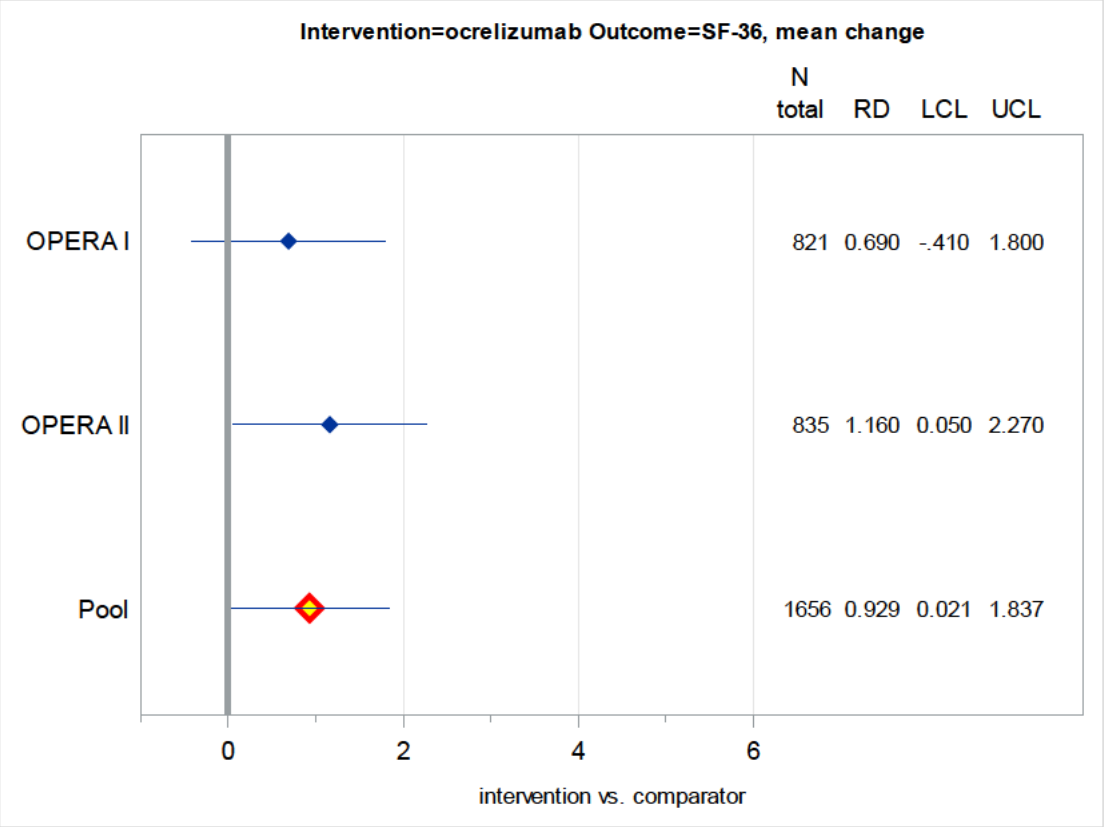
LCL, lower confidence limit; N, number of subjects; RR, relative risk; SAE, serious adverse event; UCL, upper confidence limit

Figure 10 Forest plot ocrelizumab, annualised relapse rate



LCL, lower confidence limit; N, number of subjects; RD, relative difference; UCL, upper confidence limit

Figure 11 Forest plot ocrelizumab, SF-36, mean change



LCL, lower confidence limit; N, number of subjects; RD, relative difference; SF-36, 36-item short form health survey; UCL, upper confidence limit

Cost- and budget impact model for ofatumumab in treatment of relapsing forms of multiple sclerosis (RMS)

Technical document – application for the Danish Medicines Council

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Table of content

1 Background

Novartis applies for the recommendation of the DMC concerning ofatumumab (Kesimpta®) as possible standard treatment for patients with relapsing forms of multiple sclerosis (RMS).

Ofatumumab will be available as a 20 mg solution for injection for subcutaneous administration. Ofatumumab is a fully human antibody that binds to a region distinct from that of other anti-CD20 antibodies, including the smaller and the larger loop of CD20 molecule.[1]

The benefits of ofatumumab are its ability to prevent relapses and slowing disease progression. The most common side effects are upper respiratory tract infections and injection-related reactions. Ofatumumab treatment should be initiated by physicians experienced in the management of neurological conditions.

The full indication ofatumumab:

Ofatumumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.[2]

Ofatumumab is administrated with an autoinjector in a dose of 20 mg subcutaneously (s.c). Ofatumumab is initially dosed in weeks 0, 1 and 2, followed by monthly dosing, starting in week 4. After initial instruction ofatumumab can be self-administered by the patient. Thereby, it is possible to avoid the burden of intravenous administration concerning both the patients, their caregivers, and the healthcare systems. Moreover, premedication to reduce injection-related reactions is not necessary with ofatumumab.[3]

Treatment of patients with relapsing multiple sclerosis
Pharmaceuticals used for treatment of RMS have historically been categorized into first line treatment and second line treatment by the Danish Medicines Council's (DMC) treatment guideline and drug recommendation. Second line treatments include the most effective treatments; however, these are generally also associated with more severe side effects.

However, due to the high efficacy, acceptable and manageable AE profile, and minimal monitoring burden, ofatumumab could potentially shift the treatment paradigm in the RMS population towards early use of high-efficacy treatments.

Clinical Questions:

The DMC's protocol for assessment of ofatumumab as treatment of RMS includes two clinical questions. The clinical questions are:

Clinical questions 1:

What is the value of ofatumumab compared to teriflunomide for treating adult patients with active RMS and average disease activity (first line treatment)?

- Population: Patients with average disease activity (defined by clinical and imaging features).
- Intervention: Ofatumumab 20 mg subcutaneous every 4 weeks (initial dose at day: 1, 7, and 14)
- Comparator: Teriflunomide 14 mg peroral (p.o) once daily.

Teriflunomide and dimethyl fumarate are considered clinically equivalent as 1st choice for the first line RMS treatment according to the DMC's treatment guideline, where dimethyl fumarate is 1st choice in the drug recommendation due to lower cost. Teriflunomide is chosen as the comparator, as a head-to-head study comparing ofatumumab and teriflunomide is available, which will result in the best evidence base for the comparison.[3]

Clinical question 2:

What is the value of ofatumumab compared to ocrelizumab for treating adult patients with active RMS and high disease activity (second line treatment)?

- Population: Patients with high disease activity (defined by clinical and imaging features), regardless of JCV status.
- Intervention: Ofatumumab 20 mg subcutaneous every 4 weeks (initial dose at day: 1, 7, and 14)
- Comparator: Ocrelizumab 600 mg intravenous (i.v.) every six months.

Ocrelizumab is considered clinically equivalent to fingolimod in the DMC's treatment guideline and 1st choice treatment for second line patients who are JCV-positive (2nd choice for JCV-negative patients) in the DMC's drug recommendation. Ocrelizumab is chosen as comparator as this is also an anti-CD20 therapy the mechanism of action is more or less similar to the mechanism of action of ofatumumab.[3]

The relevant comparison for the population in this application is presented in **Table 1**:

Table 1: Intervention and comparators in the model

	Administration form	Dosing	Population
Intervention			
Ofatumumab	s.c.	20 mg once monthly* (initial dose at day: 1, 7, and 14.	First- and second line treatment population
Comparators			
Teriflunomide	p.o.	14mg once daily	Clinical question 1
Ocrelizumab	i.v.	600mg every six month (the initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion	Clinical question 2

*A monthly dose has been applied since this is the approved dosing according to the SmPC of ofatumumab. Novartis has notified the DMC about the discrepancy between the dosing specified in the protocol and the approved dosing prior to this submission. It was agreed by the DMC that the monthly dosing regimen was appropriate to apply for the submission.

2 Cost per patient analysis

2.2 Model description

For clinical question 1, a simple cost-per-patient analysis was developed. With the objective of model parsimony and to avoid any unnecessary complexity, disease progression was not directly modelled, and only events such as administration, monitoring, and relapses were modelled. This approach aligns with what has been accepted by the DMC in previous submissions within RMS. Adverse events were not included, since no significant differences were demonstrated in the overall clinical safety data. A difference in injection-related systemic reactions were observed between ofatumumab and teriflunomide in ASCLEPIOS II, however the majority (99.8%) were mild to moderate in severity. Only two (0.2%) ofatumumab-treated MS patients reported serious injection-related reactions, but not life-threatening. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills and fatigue. Consequently, these adverse events are not expected to result in any meaningful difference in cost.

In the model dashboard, it is possible to select the treatment line comparison to be first line or second line. If first line treatment is selected, the cost per-patient graph will illustrate the comparison between teriflunomide and ofatumumab. If second line treatment is selected, the comparison between ocrelizumab and ofatumumab is illustrated. The cost of relapse can be included and excluded in the dashboard as well.

2.2.1 Comparators and relative efficacy

The model includes two comparators, one for each clinical question, based on the DMC's protocol for assessment of ofatumumab as treatment of RMS.[3] The two comparators included are teriflunomide and ocrelizumab.

Clinical question 1:

Based on the assessment and analysis of the clinical data, ofatumumab was found to be a clinically superior treatment option in term of annualised relapse rate (ARR) compared to teriflunomide. The difference was reported in Hauser et al., 2020,[1] which is based on the two clinical trials ASCLEPIOS I and II. The ARR was significantly lower with ofatumumab compared with teriflunomide in each of the two trials. To reflect the observed difference in ARR between the interventions, a cost per relapse and a weekly probability of relapse was included for both comparators in the base case.

Clinical question 2:

For clinical question 2, a cost-minimization analysis approach was adopted, as ofatumumab and ocrelizumab are expected to be considered clinically equivalent. Based on a narrative comparison there was no difference between ofatumumab and ocrelizumab with respect to efficacy and safety, However, ofatumumab seems to have a slightly more favorable safety profile compared with ocrelizumab. Practically this means that the ARR between ofatumumab and ocrelizumab was set to 1.

2.2.2 Resources and costing perspective

The model applies a Danish restricted societal perspective in line with DMC guidelines. All interventions are fixed-dose, and consequently no patient characteristics have been applied in this model with the objective of model parsimony.

The analysis includes drug cost, administration cost, monitoring cost, relapse costs, patient costs and transportation costs. Drug costs were accounted for by identifying the AIP at medicinpriser.dk. The Danish DRG tariff system (interaktiv DRG 2021) was used to account for administration- and monitoring cost. The DMC's methods guideline for unit cost was applied to account for patient cost.

2.2.3 Time horizon

The time horizon was chosen to be 3 years in accordance with the time horizon applied in the recent assessment of ozanimod by the DMC's for RMS patients.[4] Similar to this assessment, the assessment for ozanimod also included two clinical questions; for first line and second line respectively. In the ozanimod assessment, the clinical expert committee argued that a three-year time horizon would be appropriate to cover both first-and second line treatment of RMS. We therefore consider it appropriate to apply the same rationale for this application. The impact of varying the time horizon was assessed in scenario analyses.

Cost are discounted 3.5% per year in accordance with DMC's methods guideline.[5]

2.3 Cost

2.3.1 Drug cost

The unit costs for the included drugs are found and sourced from Medicinpriser.dk. These are applied in Table 2.

Table 2: The drug prices applied in the model (AIP DKK).

Drug	Formulation	Packing	Price*	Source
Ofatumumab	20mg	1 unit	10,800.00	Medicinpriser.dk (Kesimpta®) 031172**
Teriflunomide	14mg	28 units	8,098.51	Medicinpriser.dk (Aubagio®) 061112/142480
	14mg	84 units	24,295.51	
Ocrelizumab	300mg	1 unit	38,755.52	Medicinpriser.dk (Ocrevus®) 533363

*Identified and sourced March 30th, 2021. **The price has been submitted to DKMA, however is not yet available at Medicinpriser.dk

2.3.2 Dosing

The analysis applies the dosing scheme presented in Table 1. Thus, two units of ocrelizumab are used per infusion. For teriflunomide and ofatumumab a single unit is used per dosing. Two different packs are presented for teriflunomide, however, the cost per units does not differ between the two packs.

No wastage is assumed in the model base case since all drugs are used at fixed doses. Assumptions around potential wastage associated with patients discontinuing treatments between dispensing visits was considered too uncertain, since no guidelines exists for the number of packs the hospital pharmacy or hospital department should dispense for each visit. This is also in line with the approach adopted by the DMC for the cost comparisons in the treatment guidelines. In the comparison with teriflunomid no difference in wastage is expected as the dispensing frequency is assumed similar for ofatumumab and teriflunomid. However, in the comparison with ocrelizumab, a potential difference may occur as ocrelizumab is administered at the hospital. Consequently, a scenario analysis is presented, where one administration is wasted, corresponding to one month of use for ofatumumab.

2.3.3 Relapses

In order to reflect the incremental cost per patient appropriately, it was necessary to include relapse costs in the analysis. The cost of a relapse is applied and sourced from Rasmussen et al., 2017. The cost per relapse was reported as DKK 19,037. The cost was estimated by calculating the differences in cost of resource use between RMS patients with an EDSS score of 0-6 with relapse and patients without relapse over a 3-month period. Only aggregate costs were reported and it was therefore not possible to split the costs per cost category. The cost categories included were inpatient care, day

admission, consultations, tests, medication, community services, investments, informal care, short-term absence, and long-term sick leave. We acknowledge that sick leave and short-term absence are not appropriate to include within the DMC guideline framework, however, no alternative to Rasmussen et al., 2017 has been identified to estimate costs associated with relapses for RMS patients in Denmark. Rasmussen et al., 2017 is a recent study based on Danish patients and is therefore expected to appropriately reflect the costs of relapses in Denmark. Moreover, it is illustrated that the sick leave and absence is a rather small proportion of the overall cost per relapse, and consequently, their impact on the overall result is minor. The cost originates from second half of 2015.[6] Using the PRIS114, the cost was projected into the current net value. The consumer price index of July 2015 (100.3) and April 2021 (104.8). The cost in 2021 value was calculated as DKK 19,891 per relapse.

The clinical differences between ofatumumab and teriflunomide were reported in Hauser et al., 2020,[1] from the ASCLEPIOS I (927 participants) and ASCLEPIOS II (955 participants) trials. In ASCLEPIOS I, the ARR was 0.11 with ofatumumab and 0.22 with teriflunomide, while the corresponding rates in ASCLEPIOS II were 0.10 and 0.25.

To synthesize the available data, the rates from the two trials were pooled based on the number of participants per trial. The ARR for ofatumumab patients was calculated as 0.1049, while the ARR for teriflunomide patients was calculated as 0.2353 (HR 2.243), presented in Table 3. These rates were converted into weekly probabilities of experiencing a relapse, using the formula p=1-exp{-r*t}. In the model, the weekly probability of getting a relapse was multiplied for each arm.

Table 3: The Annualised Relapse Rates (AARs) from the two trials presented in Hauser et al., 2020, and the calculated pooled ARRs.

Drug	ARR ASCLEPIOS I	ARR ASCLEPIOS II	Pooled ARR	Source
Ofatumumab	0.11	0.22	0.1049	Hauser et al., 2020,[1]
Teriflunomide	0.10	0.25	0.2353	Hauser et al., 2020,[1]

The relapse rates of ofatumumab and ocrelizumab were assumed to be equal, referring to the assumed clinical equivalence presented in section 2.2.2.

2.3.4 Administration and monitoring (hospital cost)

Ofatumumab is intended for self-administration. It is expected that training in s.c. self-administration will be provided at the initial hospital visit. Therefore, an administration cost visit has been applied in the first model cycle for ofatumumab. For teriflunomide, the p.o. administration is not expected to result in any administration cost. Ocrelizumab is intended for administration by a healthcare professional and is administrated i.v. every six months. To reflect this, an administration cost has been applied at each administration for ocrelizumab.

Premedications are required before each administration of ocrelizumab in the form of[7]:

- 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion
- antihistamine approximately 30-60 minutes prior to each ocrelizumab infusion

In addition, premedication with an antipyretic (e.g paracetamol) may also be considered approximately 30-60 minutes prior to each ocrelizumab infusion.

In this model, costs for premedications were not included, as the costs associated with these are minimal (estimated to be DKK 225 in year one and DKK 150 in the remaining years in the DMC assessment for ocrelizumab for ppms[8]). Consequently, the exclusion of these costs is conservative in favour of ocrelizumab, however the impact on the results is expected to be negligible.

Patients are expected to be monitored according to

Table **4**. The estimations for each intervention are based on the national treatment guidelines.[9] Patients treated with ofatumumab are expected to follow the same monitoring scheme as ocrelizumab due to the similarity in the mode of action (anti-CD20 therapies). This assumption has been validated by a Danish KOL within RMS. The KOL stated that the planned control visits might be lower for ofatumumab as well as ocrelizumab in the future for well treated patients, however, as a conservative approach, the same number of monitoring visits are assumed for both treatments. The number of MRIs are expected to be the same for all three alternatives. For teriflunomide clinical control is expected to be necessary every six months for the first two years; after this once per year is the minimum. Furthermore, based on KOL testimony it is estimated that patients treated with teriflunomide should have a blood test every 1 months for the first half year of treatment; after this point a blood test every 3-6 months is needed. For ocrelizumab a clinical control is needed at 3 months and 6 months; after this, every six months. Patients treated with ocrelizumab should have a blood test 2 weeks before each administration.

Table 4: Monitoring visits for the three comparators

Drug	Ofatumumab			Teriflunomide			Ocrelizumab		
Time	1st year	2nd year	Following years	1st year	2nd year	Following years	1st year	2nd year	Following years
MRI at the hospital	2	1	1	2	1	1	2	1	1
Clinical control and EDSS status	3	2	2	2	2	1	3	2	2
Blood test	3	2	2	7	2	2	3	2	2

The frequencies of visits presented above were applied in the model along with the cost of each administration or monitoring visit. The costs were sourced from the Danish DRG 2021. The costs applied are listed below in Table 5.

Table 5: Cost applied for administration and monitoring (hospital cost). The costs are based on 2021 DRG (DKK).

Type	Price	Note	Source
MRI at the hospital	2,319.00	DRG 2021, 30PR03 MR-scanning, ukompliceret, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: (UXMA00) MR-skanning af cerebrum	DRG 2021, interaktiv DRG
Clinical control and EDSS status	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: ZZ9010: Medikamentel behandling, kontrol af	DRG 2021, interaktiv DRG
Blood test	129.00	DRG 2021, 65TE01, Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar	DRG 2021, interaktiv DRG
S.c. administration	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: BWAA31: Medicingivning ved subkutan injektion, ZZ9010: Medikamentel behandling, kontrol af,	DRG 2021, interaktiv DRG
I.v adminstration	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: BWAA62 Medicingivning ved intravenøs infusion, Behandling med ocrelizumab. Interaktiv DRG	DRG 2021, interaktiv DRG

2.3.5 Patient and transportation cost

Patient costs were included in line with DMC guideline, as DKK 179 is estimated per hour used. Patient costs were included for monitoring and administration. A monitoring visit was assumed to be one hour for all interventions. No patient time was estimated for p.o. administration and for s.c. administration 10 minutes was estimated in line with DMC's cost analysis for equivalent treatments of RMS.[10] For ocrelizumab 2.5 hours of i.v. administration and 1 hour of observation following the administration was estimated per administration in line with the DMC's recommendation of ocrelizumab.[11]

Transportation costs are included in the model in line with DMC guidelines. An average rate of DKK 3.52 per km is assumed with an average distance of 28 km per hospital visit in line with DMC's methods guideline.[12] In the model, transportation cost is applied at the occurrence of hospital visits, e.g. administration or monitoring visits.

2.4 Summary of base-case assumptions

Table 6: Summary of the assumptions applied in the base-case

Element	Base-case
Intervention	ofatumumab
Comparators	teriflunomide (first line) ocrelizumab (second line)
Time horizon	3 years (36 months)
Discount rate	3,5%
Included costs	Drug acquisition Administration Relapse Monitoring Patient time Transportation
Treatment line	First- and second line treatment
Treatment duration	3 years for all interventions
Wastage assumed	No
HR for relapse vs. ofatumumab	2,24 (teriflunomide) 1,00 (ocrelizumab)
Other key assumptions	Safety profiles are assumed similar for all included interventions Efficacy is assumed similar for ofatumumab and ocrelizumab

2.5 Results

2.5.1 Base-case

For the first line treatment population, ofatumumab represents an incremental cost of DKK 92,915 per patient compared to teriflunomide using AIP-prices over a 36-month time horizon. For the second line treatment population, ofatumumab is cost saving, as the incremental result is DKK -75,295,26 per patient compared to ocrelizumab using AIP-prices prices over a 36-month time horizon.

Ofatumumab represents a cost of DKK 444,452, teriflunomide represents a cost of DKK 351,537, and ocrelizumab a cost of DKK 519,747 using AIP prices over the 36-month time horizon.

Table 7: Base-case costs for the first line treatment population over 36 months (AIP DKK)

Drug:	Ofatumumab	Teriflunomide	Incremental vs. teriflunomide
Drug cost	397,400.38	305,281.64	92,118.74
Hospital cost	36,071.86	26,751.80	9,320.06
Relapse cost	6,385.07	15,432.86	-9,047.79
Patient cost	3,352.94	2,625.08	726.86
Transportation cost	1,241.74	1,445.41	-203.67
Total	**444,451.99**	**351,536.79**	**92,915.19**

Table 8: Base-case costs for the second line treatment population over 36 months (AIP DKK)

Drug:	Ofatumumab	Ocrelizumab	Incremental vs. ocrelizumab
Drug cost	397,400.38	449,516.64	-52,116.26
Hospital cost	36,071.86	55,517,21	-19,445.35
Relapse cost	6,385.07	6,385.07	0.00
Patient cost	3,352.94	6,515.00	-3,162.06
Transportation cost	1,241.74	1,813.32	-571.59
Total	**444,451.99**	**519,747.24**	**-75,295,26**

2.5.2 Sensitivity analyses

To investigate the impact of main variables in the analysis, scenario analyses were conducted. The following scenario analyses were conducted: the time horizon varied to 1 and 5 years, respectively, variation in relapse cost, and wastage for ofatumumab vs. ocrelizumab. The scenario analyses for the first line treatment comparison are presented in Table 9, while the scenario analyses for the second line treatment comparison are presented in Table 10.

Table 9: Scenario analysis for the pairwise comparison with teriflunomide (AIP DKK).

Scenario	Incremental cost vs. teriflunomide	Difference in percentage
Base-case ofatumumab	**92,915.19**	
The cost of a relapse is 20% higher	91,105.64	2%
The cost of a relapse is 20% lower	94,724.75	2%
Time horizon of 12 months	48,574.10	-48%
Time horizon of 60 months	137,582.63	48%

Table 10: Scenario analysis for the pairwise comparison with ocrelizumab (AIP DKK).

Scenario	Incremental cost vs. ocrelizumab	Difference in percentage
Base-case ofatumumab	**-75,295,26**	
Time horizon of 12 months	-12,187.03	-84%
Time horizon of 60 months	-109,806.82	78%
One pack (one month) of wastage applied for ofatumumab as a one-off cost in the first year	-64,495.26	-6%

The scenario analysis illustrates that assuming a ±20% difference in the cost per relapse, it has a minimal impact on the overall results (±2%). Since no treatment discontinuations are assumed in this model, changing the time horizon will naturally have a high impact on the results in either of the two analyzed populations.

3 Budget Impact model

3.1 Methods

A budget impact model (BIM) was conducted to compare the regional expenses in the current scenario (without the recommendation of ofatumumab) with the regional expenses in a future scenario with the recommendation of ofatumumab as possible standard treatment. The budget impact is presented per year over a five-year period without discounting.

The BIM is imbedded in the cost per patient model, and consequently, any updates of the assumptions in the costs per patient model will impact the results of the BIM.

In the base-case an average annual cost per patient approach has been applied as is standard in budget impact models. Using this approach, the average cost per year over the chosen time horizon is calculated and applied per year. This approach is naturally a simplification, since this will not directly reflect the cost per patient for the stratified patient cohort in any given year, however, this approach is necessary since we do not have any robust data on treatment switching for all the interventions included. By using this approach, all the interventions can compete for the total prevalent population in any given year, which aligns with the assumptions applied for the market shares. The time horizon, i.e. the calculated average treatment duration per patient, of the BIM follows the time horizon in the cost per patient model, i.e. 36 months. Alternative scenarios have been included, where the costs are based directly on the trace in the model, however this leads to implausible results, since this assumes that all prevalent patients start in year one and exit the model after 36 months. In this scenario, only incident patients will compete for the market shares in year 2 and onwards.

3.2 Comparators

To reflect the current treatment mix scenario, both teriflunomide and dimethyl fumarate were included in the BIM for the first line treatment, as dimethyl fumarate is currently first choice in the drug recommendation. With the same rationale both ocrelizumab and fingolimod were included in the BIM for the second line treatment for completeness.

Table 11: Intervention and the comparators included in the BIM.

	Administration form	Dosing	Population
Intervention			
Ofatumumab	s.c.	20mg once monthly (initial dose at day: 1, 7, and 14.	First- and second line treatment population
Comparators			
Teriflunomide	p.o.	14mg once daily	Clinical question 1
Dimethyl fumarate	p.o.	2x240mg daily (initial dose is 2x120mg daily for the first 7 days)	Clinical question 1
Ocrelizumab	i.v.	600mg every six month (the initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg)	Clinical question 2

		infusion, followed 2 weeks later by a second 300 mg infusion	
Fingolimod	p.o.	0.5mg daily	Clinical question 2

3.3 Cost

3.3.1 Drug cost

The unit cost of the drugs included in the BIM was sourced from Medicinpriser.dk using AIP-prices. These are presented in Table 12.

Table 12: The drug cost of the five treatments included in the BIM (AIP DKK).

Drug	Formulation	Packing	Price in DKK (AIP)*	Source
Ofatumumab	20mg	1 unit	10,800.00	Medicinpriser.dk (Kesimpta®) 031172
Teriflunomide	14mg	28 units	8,098.51	Medicinpriser.dk (Aubagio®) 061112/142480
	14mg	84 units	24,295.51	
Ocrelizumab	300mg	1 unit	38,755.52	Medicinpriser.dk (Ocrevus®) 533363
Dimethyl fumarate	120 mg	14 units	2,541.43	Medicinpriser.dk (Tecfidera®) 392438
	240mg	56 units	10,018.18	Medicinpriser.dk, (Tecfidera®) 400574
Fingolimod	1 mg	7 units	2,834.40	Medicinpriser.dk, (Gilenya®) 050438

3.3.2 Dosing

The analysis applies the dosing scheme presented in Table 11. For fingolimod, a single unit is used per dosing daily. For dimethylfumarate, 120mg is dosed twice daily for the first seven days, while 240mg is dosed twice daily for the remaining treatment duration. 3.3.3 Relapses

The cost of relapses was applied in the BIM using the same method as described in section 2.3.3. The relapse rates of teriflunomide and dimethyl fumarate were expected to be equal, as the two drugs are clinically equivalent in DMC's treatment guideline.[13] The relapse rates of ofatumumab, ocrelizumab, and fingolimod were expected to be equal, as these are not expected to differ between the second line treatments.

3.3.4 Administration and monitoring (hospital cost)

The cost of administration and monitoring for the BIM was estimated using the same method as described in section 2.3.4. Dimethyl fumarate and fingolimod were estimated to imply the same administration cost as teriflunomide, as all three drugs are self-administrated p.o.

The monitoring frequencies and cost from section 2.3.4 are applied for ofatumumab, teriflunomide, and ocrelizumab in the BIM as well. The frequencies for dimethyl fumarate and fingolimod are presented below in **Table *13***. Moreover, patients treated with fingolimod are expected to have an

EKG at first dose, an ophthalmological examination, and a dermatological examination at six months, 12 months, and once per year after that.

Table 13: Frequencies of monitoring visits for dimethyl fumarate and fingolimod

Drug	Dimethyl fumarate			Fingolimod		
Time	1st year	2nd year	Following years	1st year	2nd year	Following years
MRI at the hospital	2	1	1	1	0	0
Clinical control and EDSS status	3	2	2	4	2	2
Blood test	3	2	2	4	2	2

The frequencies were applied in the model along with the relevant DRG tariffs presented below.

Table 14: Unit costs applied in the budget impact model

Type	Price	Note	Source
MRI at the hospital	2,319.00	DRG 2021, 30PR03 MR-scanning, ukompliceret, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: (UXMA00) MR-skanning af cerebrum	DRG 2021, interaktiv DRG
Clinical control and EDSS status	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: ZZ9010: Medikamentel behandling, kontrol af	DRG 2021, interaktiv DRG
Blood test	129.00	DRG 2021, 65TE01, Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar	DRG 2021, interaktiv DRG
S.c. administration	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: BWAA31: Medicingivning ved subkutan injektion, ZZ9010: Medikamentel behandling, kontrol af,	DRG 2021, interaktiv DRG
I.v adminstration	3.353,00	DRG 2021, 01MA98: MDC01 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DG359A: Attakvis dissemineret sklerose Procedure: BWAA62 Medicingivning ved intravenøs infusion, Behandling med ocrelizumab. Interaktiv DRG	DRG 2021, interaktiv DRG
Ophthalmological examination	1.028,00 kr.	DRG 2021, 02PR01 Øjenundersøgelse, mindre Diagnosis: DG359A Attakvis dissemineret sklerose Procedure: UCXA Fotografiske undersøgelser af øje og øjenomgivelser	DRG 2021, interaktiv DRG

EKG	3.353,00	DRG 2021, 01MA98 MDC01 1-dagsgruppe, pat. mindst 7 år. Diagnosis: DG359A Attakvis dissemineret sklerose. Procedure: ZZ3925 EKG	DRG 2021, interaktiv DRG
Dermatological examination	3.353,00	DRG 2021, 01MA98 MDC01 1-dagsgruppe, pat. mindst 7 år. Diagnosis: DG359A Attakvis dissemineret sklerose.	DRG 2021, interaktiv DRG

3.3 Patient numbers

The first line treatment population includes patients with an average disease activity. The second line treatment population includes patients with a high disease activity which have not been treated before, and patients with persistent disease activity while being treated with first line treatment.

The number of patients eligible for first line treatment is estimated by Novartis to be 2,880 in the 1st year. The number is expected to increase to 3,300 patients in the 5th year. For second line treatment, Novartis estimated that 3,185 patients are candidates for treatment in the 1st year, which is expected to increase to 4,900 in the 5th year. The numbers are based on the annual report from Sclerosebehandlingsregistret[14]: Here 3,185 patients were in second-line treatment in 2020. The 2,880 patients in first line treatments are based on the difference between the total number of patients treated (6,515) and the number of patients in second line treatment (3,185). The annual increase in the total population is similarly based on data Sclerosebehandlingsregistret.

Table 15: Estimated patient count for both treatment populations.

	1st line treatment population						2nd line treatment population				
Year	1st year	2nd year	3rd year	4th year	5th year		1st year	2nd year	3rd year	4th year	5th year
No. of patients who candidate for treatment	2,880	2,990	3,100	3,200	3,300		3,185	3,500	3,900	4,400	4,900

3.4 Market shares

First line treatment population

In the current scenario (without recommendation of ofatumumab) it is expected that teriflunomide and dimethyl fumarate will have a market share of 50% each. As teriflunomide and dimethyl fumarate are considered clinically equivalent, the market shares will be highly dependent on the specific tender price. It is expected that the tender winner of the two will get the majority of the market. However, since the actual market share is uncertain, this simplification was applied. In any given year, this assumption might not be representative of the budget impact, however over time it will likely be more appropriate. These market shares are expected to continue in all five years.

In the scenario where ofatumumab is recommended for first line treatment, it is assumed that ofatumumab reaches a market share of 1% the first year, 3% the second year, 5% the third year, 6% the 4th year, and 7% the 5th year. As 80-95% of the first-choice treatment population will receive the 1st choice treatment (depending on anticonception and pregnancy status), the market shares of ofatumumab are expected to remain under 10% for the first five years.

The market shares for the first line treatment population are presented in Table 16.

Table 16: Estimated market shares per year

	Without recommendation of ofatumumab					With recommendation of ofatumumab				
Treatment	**1st year**	**2nd year**	**3rd year**	**4th year**	**5th year**	**1st year**	**2nd year**	**3rd year**	**4th year**	**5th year**
Ofatumumab	0%	0%	0%	0%	0%	1%	3%	5%	6%	7%
Teriflunomide	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Dimethyl fumarate	50%	50%	50%	50%	50%	49%	47%	45%	44%	43%

Second line treatment population

In the current scenario (without recommendation of ofatumumab) it is expected that ocrelizumab and fingolimod will have a market share of 40% and 59.8% the first year, respectively. Ofatumumab is expected to get a 0.2% market share the first year, which is expected to increase by 0.2% each of the remaining years. The additional market share gained by ofatumumab is taken from fingolimod.

In the scenario where ofatumumab is recommended for second line treatment, it is assumed that ofatumumab reaches a market share of 2% the 1st year, which is expected to increase by 3% each of the remaining years. As approximately 80% of the second line treatment population will receive the 1st choice treatment (JCV status), the market shares of ofatumumab are expected to remain under 20% for the first five years. The market shares for the second line population are presented in Table 17.

Table 17: Estimated market shares per year

	Without recommendation of ofatumumab					With recommendation of ofatumumab				
Treatment	**1st year**	**2nd year**	**3rd year**	**4th year**	**5th year**	**1st year**	**2nd year**	**3rd year**	**4th year**	**5th year**
Ofatumumab	0.2%	0.4%	0.6%	0.8%	1%	2%	5%	8%	11%	14%
Ocrelizumab	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%
Fingolimod	59.8%	59.6%	59.4%	59.2%	50%	58%	55%	53%	49%	46%

3.5 Results

3.5.1 Base-case

Using AIP-prices, the estimated budget impact of recommending ofatumumab as standard treatment for the first line treatment population is DKK 194,144 in year 1, DKK 604,677 in year 2, DKK 1,044,872 in year 3, DKK 1,294,293 in year 4 and DKK 1,557,196 is expected in year 5. The results are illustrated in Table 18.

Table 18: Result from the base case. Estimated budget impact per year for the next five years for first line treatment (AIP DKK).

	1st year	2nd year	3rd year	4th year	5th year
Recommended	380,860,170	395,810,031	410,789,552	424,256,544	437,737,017
Not recommended	380,666,026	395,205,353	409,744,680	422,962,251	436,179,821
Total budget impact	**194,144**	**604,677**	**1,044,872**	**1,294,293**	**1,557,196**

Using AIP-price, the estimated budget impact of recommending ofatumumab as standard treatment for the second line treatment population is expected to be approximately DKK -540,649 in year 1, DKK -1,518,305 in year 2, DKK -2,721,633 in year 3, DKK -4,232,393 in year 4 and DKK -6,007,207 in year 5. The results are illustrated in Table 19.

Table 19: Result from the base case. Estimated budget impact per year for the next five years for second line treatment (AIP DKK).

	1st year	2nd year	3rd year	4th year	5th year
Recommended	531,185,438	582,730,062	648,224,419	730,085,292	811,663,251
Not recommended	531,726,086	584,248,367	650,946,052	734,317,686	817,670,459
Total budget impact	**-540,649**	**-1,518,305**	**-2,721,633**	**-4,232,393**	**-6,007,207**

3.4.2 Scenario analysis

The result of changing the assumptions concerning market shares compared with the base case is presented in two scenario analyses. For both populations, the impact of assuming a different plausible uptake distribution is minor. The results are presented in Table 20 and Table *21*.

Table 20: Scenario analysis for the budget impact over a five-year period for first line treatment population (AIP DKK).

Scenarios	Total budget impact in year 5 (DKK)
Base-case	**1,557,196**
ofatumumab with a market share of 5% for all years teriflunomide with a market share of 47.5% for all years dimethyl fumarate with a market share of 47.5% for all years	3,161,501
ofatumumab with a market share of 10% for all years teriflunomide with a market share of 45% for all years dimethyl fumarate with a market share of 45% for all years	6,323,002

Table 21: Scenario analysis for the budget impact over a five-year period for second line treatment population (AIP).

Scenarios	Total budget impact in year 5 (DKK)
Base-case	**-6,007,207**
ofatumumab with a market share of 10% for all years ocrelizumab with a market share of 30% for all years fingolimod with a market share of 60% for all years	-11,752,666
ofatumumab with a market share of 20% for all years ocrelizumab with a market share of 40% for all years fingolimod with a market share of 40% for all years	-8,779,764

4 Conclusion

Using AIP-prices, ofatumumab is associated with a higher cost per patient compared to teriflunomide for the first line treatment of the RMS population over a 3-year time horizon, while ofatumumab is associated with a lower cost per patient compared to ocrelizumab for the second line treatment of the RMS population over a 3-year time horizon.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende ofatumumab til behandling af attakvis multipel sklerose

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

AR	*Adverse reaction*
CDP	*Confirmed Diasability Progression*
CI	*Confidence interval*
DMT	Disease Modifying Treatment
EDSS	*Expanded Disability Status Scale*
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*)
HTA	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG	*The Institute for Quality and Efficiency in Healthcare*
ITT	*Intention-to-treat*
MS	Multipel sklerose
PICO	*Population, intervention, comparator and outcome*
PP	*Per-protocol*
PPMS	Primær progressiv multipel sklerose
RCT	*Randomised clinical trial*
RMS	Relapserende multipel sklerose
RR	Relativ risiko
RRMS	Relapserende remitterende multipel sklerose
SDMT	*Symbol digit modality test*
SD	Standardafvigelse (*standard deviation)*
SPMS	Sekundær progressiv multipel sklerose

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Novartis, som ønsker, at Medicinrådet vurderer ofatumumab til attakvis multipel sklerose. Medicinrådet modtog den foreløbige ansøgning den 23. december 2020 og en opdateret version 4. februar 2021. Novartis fik forhåndsgodkendelse (positive opinion) i EMA den 28. januar 2021.

2.1 Attakvis multipel sklerose

Multipel sklerose (MS) er en kronisk inflammatorisk lidelse i centralnervesystemet, der typisk debuterer i 20-40 års alderen og rammer kvinder ca. dobbelt så ofte som mænd. I Danmark lever omkring 17.000 personer med multipel sklerose, og den årlige incidens er ca. 600 [1,2].

MS er karakteriseret ved, at flere lokaliserede områder i hjerne og rygmarv angribes af immunologiske celler og komponenter, som ødelægger myelinskeder omkring nervefibrenes udløbere (aksoner). Tab af myelinskede forringer eller ødelægger aksonets evne til at transmittere elektriske signaler og medfører nedsat ledningshastighed eller ledningsblok resulterende i neurologiske udfald. Udover at være immunmedieret er sygdommens underliggende årsag ukendt. Der er dog fundet en række genetiske, miljømæssige og livsstilsassocierede risikofaktorer [3,4].

Patienter med MS vil opleve symptomer på deres sygdom, afhængigt af hvor deres læsion befinder sig i centralnervesystemet. Disse symptomer omfatter synspåvirkning, nedsat motorisk funktion, føleforstyrrelser, nedsat balance, vandladningsforstyrrelse, forstoppelse, nedsat seksualfunktion, smerter, træthed samt nedsat hukommelse og koncentrationsevne. Patienternes livskvalitet kan være meget negativt påvirket af symptomerne på deres sygdom.

MS kan inddeles i to overordnede kategorier: attakvis MS og progressiv multipel sklerose. Attakvis MS er langt den hyppigste form for MS og er karakteriseret ved attakvise episoder med forværring af symptomer efterfulgt af perioder med bedring. Attakvis MS kan progrediere til sekundær progressiv multipel sklerose (SPMS), hvor der ses et sygdomsforløb med progressiv forværring. MS kan også kategoriseres yderligere i forhold til, om sygdommen er aktiv eller ikke-aktiv [5,6]. Med aktivitet menes der attakker eller forværring, som ses på scanninger.

2.2 Ofatumumab til behandling af attakvis MS

Ofatumumab er et fuldt humaniseret monoklonalt IgG_1 antistof, der binder specifikt til et molekyle, som kaldes CD20. CD20 er et overfladeprotein på B-celle-lymfocytter og i mindre grad på nogle T-celle-lymfocytter [7,8].

Ofatumumab virker som et B-celle-depleterende lægemiddel i lighed med andre monoklonale antistoffer rettet mod CD20, f.eks. rituximab og ocrelizumab.

Ofatumumab (Kesimpta) er tilgængeligt i form af en opløsning til subkutan injektion. Ofatumumab doseres med 20 mg om ugen de første tre uger. Herefter holdes en uges pause, før der overgås til månedlig dosering.

Ofatumumab vil være indiceret til behandling af voksne patienter med attakvise former for MS med aktiv sygdom defineret ved kliniske og/eller radiologiske undersøgelser. Indikationen omfatter nydiagnosticerede patienter med attakvis MS og patienter, der allerede er i behandling, men som skifter behandling pga. manglende effekt eller bivirkninger. Ofatumumabs indikation omfatter således både 1. og 2. linje i dansk behandlingspraksis inden for MS. Se mere i afsnittet Nuværende behandling.

2.3 Nuværende behandling

MS er en uhelbredelig sygdom, og i attakvis MS er det overordnede behandlingsformål at begrænse varighed og intensitet af det akutte atak, at symptomlindre samt at reducere frekvens og intensitet af fremtidige attakker. Derved håber man at kunne begrænse funktionstab og øge patientens livskvalitet. Behandling af attakvis MS kan således inddeles i to kategorier: symptomlindrende behandling og sygdomsmodificerende behandling (*disease modifying therapy*, DMT).

Inddeling af patienter
Lægemidler til behandling af attakvis multipel sklerose er delt op i to grupper i Medicinrådets behandlingsvejledning og lægemiddelrekommandation [9,10], hhv. første og anden linje. Dette skal forstås således, at de mest effektive og potentielt mest bivirkningstunge lægemidler kaldes andenlinjepræparater og forbeholdes patienter med størst sygdomsaktivitet eller patienter, hvor førstelinjebehandling viser sig ikke at være effektiv nok.

Patienterne, som kan behandles med lægemidler fra gruppen af førstelinjepræparater, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret klinisk og radiologisk). Skift mellem lægemidler inden for gruppen af førstelinjepræparater kan ske på grund af eksempelvis betydende bivirkninger eller ændringer i graviditetsønske.

Patienter, som behandles med førstelinjepræparater, opdeles efter graviditetsønske og anvendelse af antikonception. Baggrunden for dette er, at der anbefales forskellige udvaskningsperioder for lægemidlerne inden påbegyndt graviditet. I den nuværende behandlingsvejledning er dimethylfumarat og teriflunomid klinisk ligestillede til mænd og kvinder, som benytter antikonception [10]. I lægemiddelrekommandationen er dimethylfumarat førstevalg for populationen, som er opdelt i to grupper: ”mænd og kvinder, som anvender antikonception og ikke har graviditetsønske” og ”kvinder, som anvender antikonception og har graviditetsønske inden for ca. et år”.

Patienterne, som kan behandles med lægemidler fra gruppen af andenlinjepræparater, er:

- patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat

- patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet.

Patienter, som behandles med lægemidler fra gruppen af andenlinjepræparater, opdeles yderligere efter, om de har antistoffer for John Cunningham virus (JCV) eller ej. Baggrunden for dette er, at behandling med nogle DMT'er (hovedsageligt natalizumab) i observationelle studier har vist sig at kunne medføre øget risiko for progressiv multifokal leukoencefalopati (PML), som forårsages af JCV [1].

Udover kliniske undersøgelser bliver patienter med MS fulgt ved radiologiske undersøgelser. Fagudvalget har i Medicinrådets behandlingsvejledning for attakvis MS anbefalet magnetisk resonansscanning en gang om året [9]. På scanningen kan klinikerne se tegn på aktiv inflammatorisk aktivitet, nye og gamle læsioner samt atrofi (tab af hjernevolumen).

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 ofatumumab sammenlignet med teriflunomid for voksne patienter med aktiv attakvis MS og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

Population
Patienter med gennemsnitlig sygdomsaktivitet (defineret klinisk og radiologisk).

Intervention
Ofatumumab 20 mg subkutant hver 4. uge (initialdosis dag: 1, 7 og 14).

Komparator
Teriflunomid 14 mg p.o. x 1 dgl.

Teriflunomid og dimethylfumarat er klinisk sidestillet som 1. valg af førstelinjepræparater til denne populationen i Medicinrådets behandlingsvejledning for attakvis MS [10], mens dimethylfumerat grundet omkostninger er første valg i lægemiddelrekommandationen. Teriflunomid er valgt som komparator, da der foreligger et direkte studie af ofatumumab og teriflunomid, hvilket vil give det bedste datagrundlag for sammenligningen.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har ofatumumab sammenlignet med ocrelizumab for voksne patienter med aktiv attakvis MS og høj sygdomsaktivitet (andenlinjebehandling)?

Population
Patienter med høj sygdomsaktivitet (defineret klinisk og radiologisk), uanset anti-JCV status.

Intervention
Ofatumumab 20 mg s.c. hver 4. uge (initialdosis dag: 1, 7 og 14).

Komparator
Ocrelizumab 600 mg i.v. hver 6. måned.

Ocrelizumab er klinisk ligestillet med fingolimod i Medicinrådets behandlingsvejledning og 1. valg af andenlinjepræparater til JCV-positive patienter (2. valg til JCV-negative patienter) i Medicinrådets lægemiddelrekommandation for attakvis MS [10]. Ocrelizumab er valgt som komparator, da det har en virkningsmekanisme, som ligner ofatumumabs.

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 hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Vedvarende sygdomsforværring bekræftet efter 3 måneder (CDP3)	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter med en ændring i CDP bekræftet efter 3 mdr.	10 %-point
Bivirkninger	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever én eller flere alvorlige bivirkninger	3 %-point
			Gennemgang af bivirkningsprofil	Kvalitativ vurdering
Årlig attakrate	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Antal attakker pr. patient om året	0,1 attakker pr. patient pr. år
Kognitiv funktion	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, som undgår en 10 %-points forværring på SDMT	10 %-point
Livskvalitet	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring i MSQOL54	0,5 SD

*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. *Standard deviation* (SD).

3.3.1 Kritiske effektmål

Vedvarende sygdomsforværring (bekræftet efter 3 måneder)

Vedvarende sygdomsforværring (Confirmed Disabilty Progression (CDP)) defineres som en ændring i Expanded Disability Status Scale (EDSS)-score på 1 eller på 0,5, hvis baseline EDSS var højere end 5,5.

EDSS er en metode til at kvantificere sygdomsforværring i MS. Måleinstrumentet måler ændringer i niveau af sygdomsforværring over tid. EDSS er det instrument, der oftest bruges, både i kliniske studier og i klinikken. EDSS-skalaen går fra 0 (fuld funktion) til 10 (død). Scorer mellem 1,0-4,5 defineres ved patienter, der stadig er i stand til at gå uden nogen hjælp, hvorimod scorer mellem 5,0-9,5 er defineret ved, at patienterne ikke kan gå. Det skal dog nævnes, at EDSS ved score ≥ 5 primært måler sygdomsforværring

relateret til, om patienterne kan gå, hvorimod funktionsniveauet i overkroppen, det kognitive funktionsniveau, energiniveau og livskvalitet ikke tages i betragtning [11]. Dette effektmål er kritisk, da et centralt mål med behandlingen er at forsinke progression af sygdommen. Effektmålet CPD3 betyder, at den vedvarende sygdomsforværring opgøres som andelen af patienter, der oplever en sygdomsforværring, som fastholdes over 3 måneder. Fagudvalget forventer, at omkring 10-15 % af patienterne behandlet med nuværende dansk standardbehandling vil progrediere i løbet af to år. Den mindste klinisk relevante forskel mellem to aktive behandlinger i første linje vurderes af fagudvalget at være på 10 %-point.

Bivirkninger
Bivirkninger (adverse reactions, AR) er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer ofatumumab sammenlignet med komparator.

Kendte bivirkninger ved andre B-celle-depleterende lægemidler er infusionsreaktioner såsom kløe, udslæt, feber, kvalme, hovedpine, hoste, træthed, svimmelhed, angioødem og hypotension. Derudover viser erfaringer fra B-celle-depleterende lægemidler, at der kan være en forøget risiko for infektioner, herunder øvre luftvejsinfektioner, herpesinfektioner og HBV-reaktivering.

Fagudvalget ønsker data på nedenstående måleenheder:

Alvorlige bivirkninger
Medicinrådet finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever én eller flere alvorlige bivirkninger, er relevant for vurderingen. Da der allerede eksisterer flere effektive behandlingsalternativer, accepterer fagudvalget ikke, at en ny behandling er markant mere bivirkningstung. Medicinrådet vurderer derfor, at den mindste klinisk relevante forskel i andelen af patienter, der får alvorlige bivirkninger, er 3 %-point.

Gennemgang af bivirkningsprofil
Medicinrådet ønsker en gennemgang af ofatumumabs, teriflunomids og ocrelizumabs bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for lægemidlerne, så fagudvalget kan vurdere forskelle mellem de forskellige behandlinger.
Medicinrådet er specielt interesseret i forekomsten af alvorlige eller hyppige infektioner samt bivirkninger, der kræver hyppig monitorering såsom ændring i levertal.
Medicinrådet ønsker sikkerhedsdata på langtidseffekter (≥ 5 år) ved behandling med ofatumumab. Herunder ønskes bivirkninger angivet med særligt fokus på udvikling af neutropeni, faldende IgG-niveauer, infektioner og vaccinationsrespons.

Medicinrådet vægter den kvalitative gennemgang af bivirkninger højt i vurderingen af ofatumumab og bemærker, at der i dansk klinisk praksis lægges stor vægt på sikkerhed og tolerabilitet ved behandling af MS på første linje.

3.3.2 Vigtige effektmål

Årlig attakrate
Den årlige attakrate beskriver antal bekræftede attakker pr. patient om året. Medicinrådet betragter dette effektmål som vigtigt, da forebyggelse af attakker er et behandlingsmål i sig selv. Attakker kan medføre varige funktionstab, og fravær af attakker må forventes at have positiv indflydelse på patienternes livskvalitet.

Et attak defineres som nye eller forværring af eksisterende symptomer af mere end 24 timers varighed i fravær af feber eller infektion, forudgået af en stabil neurologisk tilstand i minimum 30 dage. Symptomerne skal desuden kunne tilskrives MS og skal være ledsaget af objektiv neurologisk forværring [12,13]. Fagudvalget har i tidligere protokoller vurderet, at de nuværende lægemidler, som anbefales til andenlinjebehandling af multipel sklerose, kan reducere den årlige attakrate med 0,2-0,5 pr. patient om året i forhold til placebo og 0,17 i forhold til interferon [1]. Medicinrådet har valgt at benytte en tilsvarende forskel for to aktive lægemidler til førstelinjebehandling. En gennemsnitlig forskel i den årlige attakrate på 0,1 pr. patient om året vurderes af fagudvalget at være den mindste klinisk relevante forskel mellem ofatumumab og komparator. Tallet kan virke meget lavt, men da velbehandlede patienter i dansk klinisk praksis generelt har få attakker (ca. 0,1- 0,2 om året ifølge upublicerede danske registerdata, som fagudvalget har kendskab til), vil en forskel på 0,1 kunne skelne mellem to behandlingers effektivitet.

Kognitiv funktion, "Symbol Digit Modality Test" (SDMT)
Medicinrådet finder, det er vigtigt at inkludere et mål for kognitiv funktion, da denne har stor betydning for patienternes trivsel og funktionsniveau. Der findes flere forskellige instrumenter, hvoraf fagudvalget har valgt SDMT-testen. I denne test skal patienterne på tid matche symboler og tal ud fra en forudbestemt nøgle. Testen er enkel, hurtig og kan med stor sensitivitet opdage kognitive skader og ændringer i kognitiv funktion over tid. Scoren bestemmes ud fra, hvor mange matchende kombinationer af symboler og tal patienterne har opnået på 90 sekunder, og kan maksimalt være 110 point [14]. En ændring i test-score på 10 % betragtes som klinisk betydningsfuld, og fagudvalget vurderer, at få patienter med gennemsnitlig sygdomsaktivitet oplever en sådan ændring på dansk standardbehandling [15]. Fagudvalget vurderer, at en forskel på 10 %-point i andelen, der ikke oplever en 10 %'s reduktion i SDMT, er klinisk relevant.

Livskvalitet, "Multiple Sclerosis Quality of Life-54" (MSQOL-54)
MSQOL-54 er et sygdomsspecifikt og valideret mål for livskvalitet, der inkluderer selvrapporterede subjektive indikatorer for fysisk, emotionel og social funktionalitet og trivsel [16,17]. MSQOL-54 bygger på det hyppigt anvendte generiske instrument til måling af livskvalitet, *Short Form 36* (SF-36). Det inkluderer alle domæner fra SF-36 og har derudover 18 sygdomsspecifikke domæner, som indeholder sundhedstilstand, seksuel funktion, tilfredshed med seksuel funktion, generel livskvalitet, kognitiv funktion, energi og social funktion. Skalaen går fra 0-100, hvor en højere score indikerer højere livskvalitet [18]. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standardafvigelse (SD) – også for patienter med MS – og

fagudvalget har derfor valgt at anvende en forbedring på 0,5 SD som mindste klinisk relevante forskel [19,20].

Såfremt der ikke foreligger data fra MSQOL-54, foretrækker Medicinrådet data fra et andet valideret instrument, som er relevant for patienter med MS, f.eks. de generiske SF-36 eller EQ-5D.

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 princippapir.

Klinisk spørgsmål 1

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor ofatumumab er sammenlignet direkte med teriflunomid. Studiet er rapporteret i følgende publikation(er):

Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020;383(6):546–57

Det er tilstrækkeligt datagrundlag til at besvare de(t) kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Klinisk spørgsmål 2

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor ofatumumab er sammenlignet direkte med ocrelizumab. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

[1] For yderligere detaljer se Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser (medicinraadet.dk)

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

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.

Valg af analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Beskriv 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.

Særlige forhold i denne protokol
Medicinrådet ønsker, at ansøger kun anvender RCT-studier til at besvare de kliniske spørgsmål i denne protokol.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk 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

Da kvinder i en fødedygtig alder udgør en væsentlig del af patienter med MS, bør ønsker om graviditet være et opmærksomhedspunkt ift. MS-behandling. Ofatumumab er et IgG-antistof og derfor i stand til at krydse placenta over i fosterets blodbane. B-celle-depleterende antistofbehandling er derfor kontraindiceret ved graviditet pga. mulig risiko for foster og nyfødt. Det anbefales, at kvinder anvender effektiv antikonception under B-celle-depleterende behandling og i minimum 6 måneder efter sidste behandling [21]. Medicinrådet vil tage overvejelser angående graviditet med i vurderingen af lægemidlet.

Medicinrådet ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer hvad angår type, varighed og forventet effekt.

8. Relation til behandlingsvejledning

Medicinrådet vil i forbindelse med vurderingen af ofatumumab tage stilling til, om lægemidlet foreløbigt kan placeres i Medicinrådets behandlingsvejledning for attakvis MS.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Kristian Storr *Overlæge, speciallæge i neurologi*	Lægevidenskabelige Selskaber og udpeget af Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde medicinrådets habilitetskrav	Region Nordjylland
Regionen ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere et medlem	Region Midtjylland
Thor Petersen *Overlæge*	Region Syddanmark
Said Nasim Ashna *Overlæge*	Region Sjælland
Jeppe Romme Christensen *Afdelingslæge*	Region Hovedstaden
Hilde Omestadt *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Elisabeth Penninga *Overlæge*	Dansk Selskab for Klinisk Farmakologi
Kan ikke opfylde medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning *Patient/patientrepræsentant*	Danske Patienter
Malene Krüger *Patient/patientrepræsentant*	Danske Patienter

Sammensætning af fagudvalg	
Preben Borring Andersen *Overlæge*	Inviteret af formanden
Matthias Kant *Overlæge*	Inviteret af formanden

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	13. april 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 1
Søgestreng til PubMed:

https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Søgetermer	Kommentar
#1	Multiple Sclerosis, Relapsing-Remitting[mh]	Søgetermer for populationen
#2	RMS[tiab] OR RRMS[tiab] OR RR-MS[tiab]	
#3	relaps*[tiab] AND (multiple sclerosis[tiab] OR MS[tiab])	
#4	#1 OR #2 OR #3	
#5	ofatumumab[nm] OR ofatumumab[tiab] OR Kesimpta*[tiab] OR Arzerra*[tiab] OR Humax*[tiab]	Søgetermer for intervention/komparator
#6	ocrelizumab[nm] OR ocrelizumab[tiab] OR Ocrevus*[tiab]	
#7	#5 OR #6	
#8	#4 AND #7	Kombination population og lægemidler
#9	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans[mh])	Filter til identificering af randomiserede studier
#10	#8 AND #9	
#11	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR case report[ti]	Eksklusion af irrelevante publikationstyper
#12	#10 NOT #11	Endelig søgning

Felter:
mh: Indekseringsterm i Medline/PubMed
ti: titel
tiab: titel/abstract
nm: supplementary concept/substance
pt: publikationstype

Søgestreng til CENTRAL:

https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
#1	[mh "Multiple Sclerosis, Relapsing-Remitting"]	Søgetermer for populationen
#2	multiple sclerosis:kw and embase:an and relaps*:ti,ab,kw	
#3	(RMS or RRMS OR "RR MS"):ti,ab	
#4	(relaps* and (multiple next sclerosis or MS)):ti,ab	
#5	#1 OR #2 OR #3 OR #4	
#6	(ofatumumab or Kesimpta* or Arzerra* or Humax*):ti,ab,kw	Søgetermer for intervention/komparator
#7	(ocrelizumab or Ocrevus*):ti,ab,kw	
#8	#6 or #7	
#9	#5 and #8	Kombination population og lægemidler
#10	(clinicaltrials.gov or trialsearch):so	Eksklusion af irrelevante publikationstyper
#11	NCT*:au	
#12	("conference abstract" or review):ti,pt	
#13	(abstract or conference or meeting or proceeding*):so	
#14	#10 or #11 or #12 or #13	
#15	#9 not #14	Endelig søgning

Felter:
mh: Medline/PubMed indekseringsterm
ti: titel
ab: abstract
kw: indekseringsterm (Medline og/eller Embase)
pt: publikationstype
so: source
au: forfatter