Medicinrådet

Bilag til Medicinrådets anbefaling vedr. talquetamab til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere behandlingslinjer

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. talquetamab
2. Forhandlingsnotat fra Amgros vedr. talquetamab
3. Ansøgers endelige ansøgning vedr. talquetamab

Johnson&Johnson

Janssen-Cilag A/S
jnj.com

27. September 2024

Til Medicinrådet

Hermed Johnson & Johnsons tilbagemelding på Medicinrådets udkast til vurdering af talquetamab til patienter med knoglemarvskræft

Vi ønsker at henlede opmærksomhed på to punkter forud for Rådets stillingtagen den 23. oktober:

1. **Overlevelsesgevinst ved talquetamab**

I rapporten præsenteres to scenarier for sammenligning af talquetamab og teclistamab, som begge er bispecifikke behandlinger, men rettet mod forskellige tumoroverflademarkører – henholdsvis GPRC5D og BCMA.

I scenarie 1 udføres en *cost-utility-analyse* af talquetamab, hvor OS, PFS og TTD fremskrives baseret på data fra MonumenTAL-1 og MajesTEC-1 studierne.

I Scenarie 2 reduceres sammenligningen til en omkostningsanalyse med ekstrapolerede data, hvor det antages, at behandlingerne er ligestillede med hensyn til effekt og bivirkninger.

I cost-utility-analysen (scenarie 1) viser resultaterne en ikke-ubetydelig QALY-gevinst på 0,99 QALY for talquetamab sammenlignet med teclistamab, svarende til 1,39 flere leveår.

Vi forstår jeres rationale bag scenarie 2, som er, at det er usikkert, om der er en overlevelsesgevinst ved talquetamab-behandling, da forskellen i overlevelse muligvis *kan* tilskrives, at MajesTEC-1-studiet blev gennemført under COVID-19-pandemien.

Vi finder det derfor relevant at informere om, [redacted]

[redacted]

Dette understøtter plausibiliteten af en overlevelsesgevinst ved talquetamab og validiteten af cost-utility-analysen, hvilket bidrager til scenarie 1 som et pålideligt beslutningsgrundlag.

Da MajesTEC-1 og MonumenTAL-1 er to sammenlignelige studier i to sammenlignelige patientkohorter, har vi i denne ansøgning nøje fulgt de samme antagelser som Medicinrådet anvendte i vurderingen af teclistamab. Herunder de tidsasfhængige nytteværdier fra MajesTEC-1. Det undrer os at disse er godtaget som pålidelige i teclistamab-vurderingen, men afvist som upålidelige i talquetamab-vurderingen. Fra vores perspektiv er der tale om to meget sammenlignelige sager, der muliggår vurdering på samme parametre.

2. Real-world data af bispecifikke behandlinger

U/sikkerhed omkring effekt og sikkerhed ved behandling med talquetamab er et gennemgående emne i rapporten; dette i forhold til det tilgængelige datagrundlag samt det forhold, at bispecifikke antistoffer er en ny behandlingsmodalitet til patienter med myelomatose og den kliniske erfaring med sikkerhed og effekt derfor - per se - er begrænset.

De samme overvejelse gjorde sig gældende i forbindelse med vurderingen af teclistamab. Derfor forudsatte Medicinrådets anbefaling af teclistamab også, at der i klinikken systematisk indsamles effekt- og bivirkningsdata for patienter, som behandles med teclistamab; hvilket er i gang og forløber som planlagt.

[redacted]

[redacted]

[redacted]

[redacted]

I har hermed mulighed for systematisk at følge op på effekten af talquetamab efter en anbefaling, [redacted]

På vegne af Johnson & Johnson

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20-09-2024

CAF/MGK/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.10.2024
Leverandør	Janssen-Cilag (Johnson & Johnson)
Lægemiddel	Talvey (talquetamab)
Ansøgt indikation	Talquetamab er indiceret som monoterapi til behandling af voksne patienter med recidiverende og refraktær myelomatose, som har fået mindst tre tidligere behandlinger, herunder med et immunmodulerende middel, en proteasomhæmmer og et anti-CD38-antistof, og som har vist sygdomsprogression under den sidste behandling.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet to forskellige pristilbud på Talvey (talquetamab):

Tilbud 1, tabel 1, gælder ved en anbefaling, med dataopsamling og med mulighed for genforhandling af prisen i forbindelse med opfølgning på dataopsamlingen.

Tabel 1: [redacted]

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Talvey	2 mg/ml	1,5 ml inj.væske, opløsning	2.831,05	[redacted]	[redacted]	[redacted]
Talvey	40 mg/ml	1 ml inj.væske, opløsning	37.747,30	[redacted]	[redacted]	[redacted]

Tilbud 2, tabel 2, gælder både hvis Medicinrådet anbefaler Talvey uden krav om dataopsamling, og hvis Medicinrådet anbefaler Talvey med dataopsamling, men er uden mulighed for genforhandling.

[redacted]

Tabel 2: [redacted]

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Talvey	2 mg/ml	1,5 ml inj.væske, opløsning	2.831,05	[redacted]	[redacted]	[redacted]
Talvey	40 mg/ml	1 ml inj.væske, opløsning	37.747,30	[redacted]	[redacted]	[redacted]

Hvis Medicinrådet ikke anbefaler Talvey, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

Amgros har en aftale på Talvey i perioden fra den 01.01.2024 til den 30.09.2025, med mulighed for prisregulering og forlængelse i 6 måneder. Prisen vil blive justeret med virkning fra 5. november 2024 afhængigt af Medicinrådets anbefaling som vist i tabel 1 og 2.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 3 viser lægemiddeludgifter pr. år for Talvey samt komparator Tecvayli (teclistamab) jf. Medicinrådets vurderingsrapport. Tecvayli (teclistamab) blev anbefalet af Medicinrådet til samme indikation i februar 2024. Elrexfio (elranatamab) er også under vurdering i Medicinrådet til behandling af knoglemarvskræft i 4. linje. Medicinrådet har udarbejdet en behandlingsvejledning vedrørende knoglemarvskræft, denne inkluderer dog ikke lægemidler til behandling i 4. linje.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)**
Talvey *Tilbud 1*	40 mg/ml	1 ml	Uge 1: Step-up dosis 1 0,01mg/kg SC Step-up dosis 2 0,06 mg/kg SC Step-up dosis 3 0,4 mg/kg SC Første vedligeholdelsesdosis dag 7, 0,8 mg/kg SC Derefter 0,8 mg/kg hver 2. uge SC	[redacted]	[redacted]
Talvey *Tilbud 2*	40 mg/ml	1 ml	Uge 1: Step-up dosis 1 0,01mg/kg SC Step-up dosis 2 0,06 mg/kg SC Step-up dosis 3 0,4 mg/kg SC Første vedligeholdelsesdosis dag 7, 0,8 mg/kg SC Derefter 0,8 mg/kg hver 2. uge SC	[redacted]	[redacted]
Tecvayli (teclistamab) *Ved komplet respons*	10 mg/ml	3 ml	Uge 1 – Step-up-dosis 1 0,06 mg/kg SC Step-up-dosis 2 0,3 mg/kg SC	[redacted]	[redacted]
Tecvayli (teclistamab) *Ved komplet respons*	90 mg/ml	1,7 ml	Uge 1-26: 1,5 mg/kg hver uge SC Uge 27-51 1,5 mg/kg hver 2. uge SC	[redacted]	[redacted]
Tecvayli (teclistamab) *Ingen komplet respons*	10 mg/ml	3 ml	Uge 1 – Step-up-dosis 1 0,06 mg/kg SC Step-up-dosis 2 0,3 mg/kg SC	[redacted]	[redacted]

Lægemiddel	Styrke	Pakningsstørrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)**
Tecvayli (teclistamab) *Ingen komplet respons*	90 mg/ml	1,7 ml	Uge 1-51: 1,5 mg/kg hver uge SC	[redacted]	[redacted]

*Gennemsnitsvægt 75 kg jf. Medicinrådets vurderingsrapport

**Beregningerne er baseret på mg. Lægemiddeludgifterne per år tager ikke højde for spild.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

[redacted].

Application for the assessment of Talvey® (talquetamab) monotherapy for the treatment of triple-class exposed relapsed and refractory multiple myeloma

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

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Abbreviations

Abbreviation	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike Information Criteria
AIP	Apotekernes indkøbspris
ASTCT	American Society for Transplantation and Cellular Therapy
ATE	Average treatment effect
ATO	Average treatment effect in the overlap
ATT	Average treatment effect in the treated
BCMA	B-cell maturation antigen
BIC	Bayesian Information Criteria
BSA	Body surface area
CAR-T	Chimeric antigen receptor T
CBR	Clinical benefit rate
CEAC	Cost-effectiveness acceptability curves
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
d	Dexamethasone
DK	Denmark
DKK	Danish crowns
DLT	Dose-limiting toxicity
DMC	Danish Medicines Council
DMSG	Dansk Myelomatose Studie Gruppe
DOR	Duration of response
DP	Disease progression
DRG	Diagnosis Related Group
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EPAR	European public assessment report
EQ-5D-3L	EuroQol Questionnaire, Five Dimensions, Three Levels

EQ-5D-5L	EQ-5D-5L = EuroQol Five Dimension Five Level Questionnaire
ESS	Effective sample size
FLC	Free light chain
FUP-Pre	Follow-up visit prior to start of subsequent antimyeloma therapy
FUP-Post	Follow-up visit on or after start of subsequent antimyeloma therapy
GHS	Global Health Status
GLOBOCAN	Global Cancer Incidence, Mortality, and Prevalence
HEOR	Health economics and outcomes research
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
HSUV	Health state utility values
HTA	Health technology appraisal
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
IL	Interleukin
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IMID	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IRC	Independent review committee
ISS	International staging system
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K	Carfilzomib
KM	Kaplan-Meier
KOL	Key opinion leader
LDH	Lactate dehydrogenase
LOT	Line of therapy
LS	Least square
MAE	Mean absolute error
MAIC	Matching-adjusted indirect comparison
MGUS	Monoclonal gammopathy of undetermined significance
MICE	Multiple imputation by chained equations
MM	Multiple myeloma
MMRM	Mixed-model repeated measures
MR	Minimal response
MRD	Minimal residual disease
MSE	Mean square error

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
N_{OBS}	Number of observations
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAA	Proline, alanine, alanine
PC	Physician's choice
PD	Progressive disease
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PI	Protease inhibitor
PPE	Palmar-plantar erythrodysesthesia syndrome
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcome
PS	Propensity score
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCC	Response review committee
RCT	Randomized controlled trial
RD	Rate difference
RDI	Relative dose intensity
RMSE	Root mean square error
RR	Response-rate ratio
RRC	Response Review Committee
RRMM	Relapsed/refractory multiple myeloma
RWE	Real-world evidence
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMD	Standardized mean difference
SOC	Standard of care
TCE	Triple-class exposed
TEAE	Treatment-emergent adverse event
TLR	Targeted literature review
TTTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTR	Time to response
US	United States

V	Bortezomib
VAS	Visual Analog Scale
VBA	Visual Basic for Applications
VGPR	Very good partial response

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Talvey
Generic name	Talquetamab
Therapeutic indication as defined by EMA	Talquetamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (EMA 2023b)
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	L01FX29
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	21 August 2023
Has the pharmaceutical received a conditional marketing authorization?	Yes. Submission of results from study 64407564MMY3002, a Phase 3 RCT comparing talquetamab in combination with daratumumab and pomalidomide (Tal-DP) or talquetamab in combination with daratumumab (Tal-D) versus daratumumab, pomalidomide and dexamethasone (DPd), in RRMM, by April 2027, and provide updated safety report from MonumenTAL-1 study by September 2024
Accelerated assessment in the European Medicines Agency (EMA)	Yes
Orphan drug designation (include date)	Yes (20 August 2021)
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	No

Overview of the pharmaceutical	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Talquetamab is available in the following packs: • Each 1.5 mL vial contains 3 mg of talquetamab (2 mg of talquetamab per mL) • Each 1.0 mL vial contains 40 mg of talquetamab (40 mg of talquetamab per mL)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Talquetamab, as monotherapy, is indicated for the treatment of adult patients with RRMM, who have previously received at least three prior therapies, including a PI, an IMiD, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (EMA 2023a, Janssen 2022f).
Dosage regiment and administration:	After a step-up phase, talquetamab is recommended at a dosing of 0.4 mg/kg Q1W or 0.8 mg/kg Q2W. This submission only considers the dosing of 0.8 mg/kg Q2W, as this is expected to be dosing used in Danish clinical practice. This dosing was the main dosing schedule used in the early access program.
Choice of comparator	Teclistamab monotherapy. Teclistamab is indicated as monotherapy for the treatment of adult patients with RRMM, who have previously received at least three prior therapies, including a PI, an IMiD, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Prognosis with current treatment (comparator)	As MM progresses, each subsequent line of therapy is associated with shorter PFS and a decreased rate, depth, and durability of response. With teclistamab mOS have been estimated to 21.9 months.
Type of evidence for the clinical evaluation	ITC (matched adjusted comparisons conducted using IPTW)

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	Progression-free survival (PFS), adjusted hazard ratio (HR) comparing talquetamab and teclistamab: [redacted] Overall survival: Adjusted hazard ratio (HR) comparing talquetamab and teclistamab: [redacted]
Most important serious adverse events for the intervention and comparator	Talquetamab: anemia grade 3+ (27.6%), CRS grade 1-2 (73.8%), CRS grade 3+ (0.7%), febrile neutropenia grade 3+ (0.7%), hypokalemia grade 3+ (5.5%), neutropenia grade 3+ (22.1%), pneumonia grade 3+ (2.1%) and thrombocytopenia grade 3 (18.6%). Teclistamab: anemia grade 3+ (37.6%), CRS 1-2 (71.5), CRS 3+ (0.6%), febrile neutropenia grade 3+ (3.6%), hypokalemia grade 3+ (4.8%), neutropenia grade 3+ (65.5%), pneumonia grade 3 (13.3%) and thrombocytopenia grade 3+ (22.4%).
Impact on health-related quality of life	No significant differences in health-related quality of life between patients treated with talquetamab and teclistamab have been identified. The health economic model uses health state specific utilities, based on the MajesTEC-1 study.
Type of economic analysis that is submitted	A cost-utility analysis was conducted based on a partitioned survival model with three health states: pre-progression, post-progression, and death
Data sources used to model the clinical effects	MonumenTAL-1 informed the clinical effect for talquetamab, and MajesTEC-1 the clinical effect of teclistamab.
Data sources used to model the health-related quality of life	MajesTEC-1 informed health-related quality of life in pre-progression and post-progression health states. External data sources were used to informed utility decrements due to adverse events
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	1,181,359 DKK
ICER (DKK/QALY)	1,059,729 DKK/QALY
Uncertainty associated with the ICER estimate	Change in the PFS utility and distribution for extrapolation of the OS and PFS curves
Number of eligible patients in Denmark	Incidence: 76 (assuming that 12% of incident MM patients have had three prior therapies, including a PI, IMiD and anti-CD38 mAb)

Summary	
	Prevalence: 3,408 patients with MM (2020). A low number expected to have had three therapies, including a PI, IMiD and anti-CD38 mAB
Budget impact (in year 5)	51,691,875 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

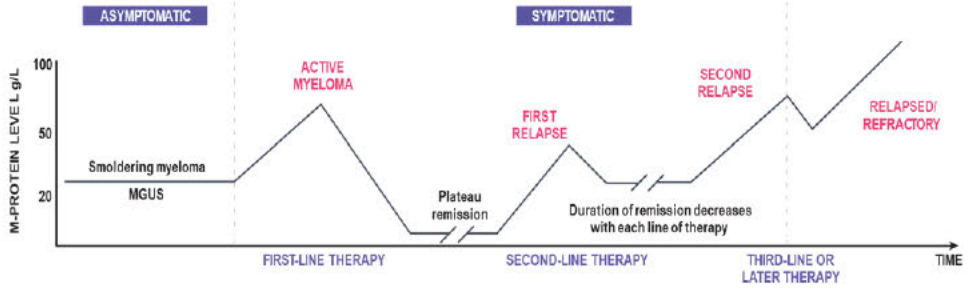
3.1 The medical condition

3.1.1 Multiple Myeloma

Multiple Myeloma (MM) is a rare and genetically complex haematological cancer (Kyle and Rajkumar 2009) that forms in the plasma cells, which are responsible for the production of antibodies, and is characterized by the overproduction of M protein.

Overproduction of M protein (an antibody) can lead to bone lesions, increased susceptibility to infections, anaemia, hypercalcemia, and renal insufficiency (Kyle and Rajkumar 2009). Due to heterogeneity, MM can take a different clinical course in different patients, although the disease is typically characterised by multiple relapses, with patients becoming refractory to treatment over time (Kurtin et al. 2013) (Figure 1).

Figure 1. Trajectory of MM and RRMM—cycles of response, remission, and relapse in the presence of treatment and clonal evolution



Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; RRMM=relapsed or refractory multiple myeloma.
Source: (Kurtin et al. 2013)

The terms ‘relapsed’ and ‘refractory’ are used to define MM patient populations in relation to the sensitivity of their disease to previous treatment:

- Relapsed MM is defined as previously treated MM that progresses and requires initiation of salvage therapy but does not meet criteria for refractory MM.
- Refractory MM is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy (Rajkumar et al. 2011).

3.1.2 Burden of disease

Although the introduction of PIs, IMiDs and mAbs during the last decade has changed the landscape of MM, leading to improved disease control and prolonged survival, as previously described, nearly all patients with MM will eventually experience relapse and become refractory to available therapies with only about half of diagnosed patients remaining alive at five years (Kurtin et al. 2013, Rajkumar et al. 2011). Approximately 4% to 12% of MM patients have been estimated to be triple class exposed (Mehra et al. 2020, Jagannath et al. 2021, Haefliger et al. 2021). There are limited data on triple class exposed RRMM, although the existing data point towards a particularly poor prognosis (Mehra et al. 2020, Terpos et al. 2018), and a high unmet need for effective therapies (Hari et al. 2018, MacEwan et al. 2018). As MM progresses, each subsequent line of therapy is associated with shorter PFS and a decreased rate, depth, and durability of response (Elsada et al. 2021, GLOBOCAN 2018, Gregory et al. 2018, Kumar et al. 2014, Lokhorst et al. 2010, Moreau et al. 2015).

With conventional therapies, mOS ranges from only 8.2 months to 15.7 months (Gandhi et al. 2019, Weisel et al. 2021, Mehra et al. 2020, Mateos et al. 2022b). Only a few studies have evaluated long-term survival outcomes in this population. Notably, low response rates are associated with a rapid decline in OS. For example, among the 12.5% of patients with very good partial response (VGPR) or better in the prospective RWE study LocoMMotion, the mOS was not yet reached, compared with a median OS of 10.9 months in the remaining 87.5% of patients without ≥VGPR (Mateos et al. 2022b).

Studies of HRQoL indicate that patients with RRMM have worse HRQoL than individuals in the general population, and those with other cancer types (Ludwig et al. 2020, Ramsenthaler et al. 2016, Kamal et al. 2021). Additionally, overall HRQoL has been found to deteriorate significantly with each relapse and increasing lines of therapy as well as with each additional year that a patient has MM (measured by EORTC-QLQ-C30 GHS) (Despiégel et al. 2019, Mateos et al. 2022a, Delforge et al. 2022, Rizzo et al. 2014).

In addition to their poor prognosis, poor HRQoL and limited effective treatment options, patients with MM also experience substantial costs associated with the disease. Overall, the lack of efficacious treatments for triple class exposed RRMM means that most patients will initiate additional lines of therapy and continue to incur high healthcare resource utilization and associated costs (Madduri et al. 2021).

In conclusion, Triple class exposed RRMM patients have a poor prognosis and high unmet need for well-tolerated therapies with novel mechanisms of action that can prolong survival and improve HRQoL. However, the novel agent teclistamab (mOS 21.9 months) was recently approved for reimbursement in Denmark. The prognosis for these patients is therefore expected to improve compared to historical data.

3.2 Patient population

The prevalence and incidence of MM in Denmark from 2017-2021 is presented in Table 1. In 2021 there were 632 patients diagnosed with MM of which 56% were males. Based on these MM data from NORDCAN, it is not possible to derive incidence rates at each relapse. However, it is known that the majority of patients with MM eventually experience disease relapse, and approximately 20% of patients die between each subsequent line of therapy (Elsada et al. 2021, GLOBOCAN 2018, Gregory et al. 2018, Kumar et al. 2014, Lokhorst et al. 2010, Moreau et al. 2015). The number of patients in Denmark with prior exposure to a PI, an IMiD, and an anti-CD38 mAb (i.e., triple class exposed) is expected to be relatively small.

Table 1. Incidence and prevalence of MM in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	537	552	607	564	632
Prevalence in Denmark	2,665	2,852	3,106	3,332	3,577

* For small patient groups, also describe the worldwide prevalence.
Source: (NORDCAN 2.0 2023b, NORDCAN 2.0 2023a, NORDCAN 2.0 2022)

To estimate the number of patients who would be eligible for the treatment with talquetamab, the reported incidence and prevalence were used along with assumptions made by Janssen. The assumption is that 12% of the incident MM patients, approximately 70 patients annually, have had three prior therapies and are assumed to have received a PI, IMiD, and anti-CD38 mAb (Haefliger et al. 2021). Of eligible patients, 15% (11 patients) are expected to receive talquetamab in the first year on the market (2024). In the following years the market share of talquetamab is expected to amount to 25%, 30% and 40% in 2025, 2026 and 2027, respectively (see Table 2).

Table 2. Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	11	18	21	28	28

Sources: Janssen internal assumption.

The target population in this assessment consist of adult Danish patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI and an anti-

CD38 mAb, and have demonstrated disease progression on the last therapy and is in line with the approved indication for talquetamab and the MonumenTAL-1 trial population. This will position talquetamab as a fourth- or subsequent-line treatment.

The baseline characteristics used in the cost-effectiveness analysis were based on the "all treated population" of the MajesTEC-1 (Phase 1+2 trial) presented in Table 3. A justification for using the MajesTEC-1 population is presented in section 6.1.3.

Table 3. Baseline characteristics: MonumenTAL-1

Characteristic	Cohort C (n=145)
Age, mean (SD)	63.9 (9.6)
Proportion female	41.8%
Body weight, mean (SD)	75.9 (16.7)

Abbreviations: SD, Standard deviation.

Source: **(Janssen 2023c)**

Subgroup analyses in both the primary analysis and the efficacy update of MonumenTAL-1 demonstrated that the response was generally consistent across most clinically relevant subgroups, including demographic and clinical characteristics, number of prior LOTs, refractoriness to prior therapy, cytogenetic risk at baseline, and baseline GPRC5D expression (Janssen 2022e, Janssen 2022a). Hence, there are no subgroups of patients where the pharmaceutical is expected to have a different efficacy and safety than anticipated for the entire population.

3.3 Current treatment options

The choice of treatment for a patient with RRMM is complicated and can be affected by many factors, including duration and depth of response to prior therapy, previous drug-related toxicities, cytogenetic abnormalities, and performance status (Dansk Myelomatose Studie Gruppe (DMSG) 2022). For most patients, treatment involves switching to a new regimen with a different mechanism of action or one or more novel agents that have been approved for MM in recent years. Key treatment aim for MM is to reduce symptoms and to delay disease progression, which is related to treatment response (Kumar et al. 2014, Ramsenthaler et al. 2016).

In Denmark, evidence-based treatment guidelines for MM are provided by DMC and The Danish Myeloma Study Group (DMSG) (Dansk Myelomatose Studie Gruppe (DMSG) 2022, Medicinrådet 2023b). The most recent treatment guidelines for MM from DMC, are valid from 6th of February 2023. The guidelines provide treatment recommendations for the first three lines of therapy (primary treatment, first relapse and second relapse), as well as fourth line and subsequent lines. For patients with RRMM, relevant treatments were considered the ones used from first relapse (Medicinrådet 2023b).

Recommended treatment regimens per line of therapy are as follows (Medicinrådet 2023b):

- In second line treatment (first relapse):
    - Patients responsive to lenalidomide: daratumumab plus lenalidomide and dexamethasone (DRd)
        - If daratumumab is contraindicated: carfilzomib plus lenalidomide and dexamethasone (KRd) OR (as second alternative) elotuzumab plus lenalidomide and dexamethasone (ERd)
        - Other regimens can be considered, such as ixazomib plus lenalidomide and dexamethasone (IRd), OR daratumumab plus bortezomib and dexamethasone (DVd), OR pomalidomide plus bortezomib and dexamethasone (PVd), OR carfilzomib and dexamethasone (Kd)
    - Patient refractory to lenalidomide but responsive to daratumumab: daratumumab plus bortezomib and dexamethasone (DVd)
- In third line treatment (second relapse) - Treatment selection should take into account refractoriness, toxicity, comorbidity and patient preference:
    - Pomalidomide-containing regimens: pomalidomide and dexamethasone (Pd) OR pomalidomide plus bortezomib and dexamethasone (PVd) OR pomalidomide plus cyclophosphamide and dexamethasone (PCd)
    - carfilzomib-containing regimens: carfilzomib plus dexamethasone (Kd)
    - Other regimens to be considered: Daratumumab monotherapy (D)

- In fourth line treatment (third relapse or higher) - Treatment selection should take into account refractoriness, toxicity, comorbidity and patient preference. The carfilzomib and pomalidomide containing regimens used in third line are recommended also in fourth line treatment:
    - Pomalidomide-containing regimens: pomalidomide and dexamethasone (Pd), pomalidomide plus bortezomib and dexamethasone (PVd) and pomalidomide plus cyclophosphamide and dexamethasone (PCd) OR carfilzomib-containing regimens: carfilzomib plus dexamethasone (Kd) and carfilzomib plus lenalidomide and dexamethasone (KRd)

Not yet mentioned within the treatment guidelines is teclistamab, a T-cell redirecting bispecific antibody that targets both B-cell maturation antigen (BCMA) and CD3, which was recently reimbursed by the Danish Medicines Council (February 21st, 2024) for treatment of patients with at least three prior therapies and triple-class exposed (Medicinrådet 2024).

3.4 The intervention

Table 4. Overview of talquetamab

Overview of talquetamab	
Mechanism of action	Talquetamab is a humanized immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) bispecific antibody directed against GPRC5D on multiple myeloma cells and the CD3 receptor on T cells (EMA 2023a, Janssen 2022f). Talquetamab

Overview of talquetamab	
	promotes enhanced T cell-mediated cytotoxicity through recruitment of CD3-expressing T cells to GPRC5D-expressing cells. This leads to the activation of T cells and induces subsequent lysis of GPRC5D-expressing cells mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. Based on the expression of GPRC5D, talquetamab targets multiple myeloma cells particularly, thus reducing potential off-target effects toward other cell lineages
Therapeutic indication relevant for the assessment	Talvey (talquetamab) is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (EMA 2023b)
Method of administration	Talquetamab is a colourless to light yellow preservative-free solution for injection. Talquetamab should be administered by subcutaneous (SC) injection by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS
Dosing	Biweekly dosing schedule: • Day 1: 0.01 mg/kg • Day 3: 0.06 mg/kg • Day 5: 0.4 mg/kg • Day 7: 0.8 mg/kg • Once every second week thereafter: 0.8 mg/kg
Dosing in the health economic model (including relative dose intensity)	0.8 mg/kg biweekly (Q2W) dosing schedule: • Day 1: 0.01 mg/kg • Day 3: 0.06 mg/kg • Day 5: 0.4 mg/kg • Day 7: 0.8 mg/kg Once every second week thereafter: 0.8 mg/kg Relative dose intensity 100% 3.80% of administrations skipped
Should the pharmaceutical be administered with other medicines?	Talquetamab is used as monotherapy. However, the following pretreatment medications should be administered 1 to 3 hours before each dose of talquetamab during the step-up phase to reduce the risk of CRS (EMA 2023a, Janssen 2022f): • Corticosteroid (oral or intravenous dexamethasone, 16 mg or equivalent) • Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent) • Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)
Treatment duration / criteria for end of treatment	Talquetamab should be continued until disease progression or unacceptable toxicity

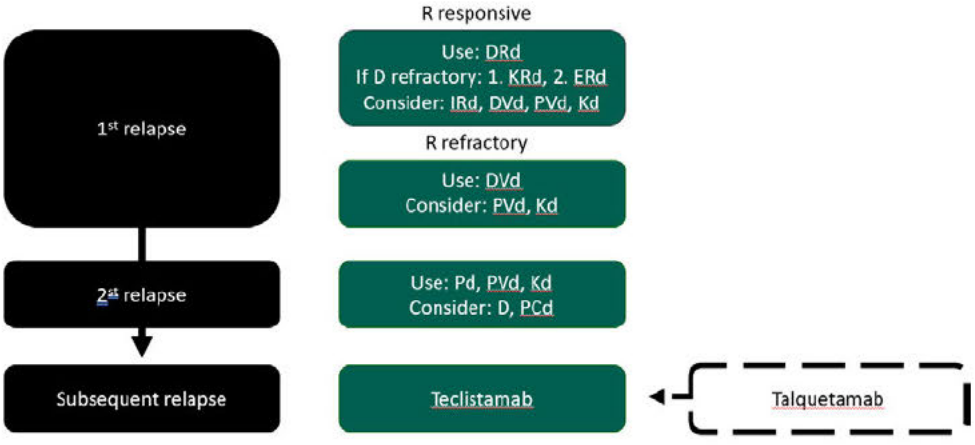
Overview of talquetamab	
Necessary monitoring, both during administration and during the treatment period	Due to the risk of CRS, patients should remain within proximity of a healthcare facility and be monitored signs and symptoms daily for 48 hours after administration of all doses within the talquetamab step-up dosing schedule.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No specific diagnostic or test is required that is not already part of clinical practice
Package size(s)	Talquetamab is available in the following packs: • Each 1.5 mL vial contains 3 mg of talquetamab (2 mg of talquetamab per mL) • Each 1.0 mL vial contains 40 mg of talquetamab (40 mg of talquetamab per mL) Talquetamab 2 mg/mL vial and 40 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration

3.4.1 The intervention in relation to Danish clinical practice

Change to current treatment algorithm:

Figure 2 summarizes the change to current treatment algorithm of RRMM in the Danish treatment landscape and where talquetamab should be used. It is expected that talquetamab will be used according to the approved indication, i.e., for the treatment of triple class exposed RRMM after at least three prior therapies including an IMiD, a PI and an anti CD38 mAb and which have demonstrated disease progression on the last therapy (EMA 2023b, Janssen 2023a), which will place talquetamab as an option for subsequent relapse.

Figure 2. Change to current treatment algorithm



V = velcade (bortezomib), C = Sendoxan (cyclophosphamide), d = dexamethasone, R = Revlimid (lenalidomide), K = Kyprolis (carfilzomib), D = Darzalex (daratumumab), I = Ninlaro (Ixazomib), E = Empliciti (elotuumab), P = Imnovid (pomalidomide)

Note: This figure only represents the talquetamab positioning in relation to the current treatment guidelines (Dansk Myelomatose Studie Gruppe (DMSG) 2022, Medicinrådet 2023b) and the recent approval by Danish Medicines Council (Medicinrådet 2024). Furthermore, second line treatment options can be used in third and later lines of treatment, if the patient is not refractory or intolerant to treatment regimen.

3.5 Choice of comparator(s)

3.5.1 Choice of comparator(s)

As previously mentioned, on February 21st (2024) the Danish Medicine Council reimbursed teclistamab for treatment of triple-class exposed patients who have received at least three prior therapies (Medicinrådet 2024); this patient population coincides with the indication of Talquetamab (EMA 2023a). DMC has assessed that teclistamab, now SOC, is the relevant comparator for talquetamab.

Because MonumenTAL-1 is a single-arm trial, an external data source is needed to estimate the efficacy of the comparator (teclistamab). The most relevant source to estimate the efficacy and safety of teclistamab is its pivotal trial, MajesTEC-1; to date MajesTEC-1 is the only trial for which teclistamab has a regulatory approval. The inclusion criteria of MajesTEC-1 were not identical to MonumenTAL-1 but comparable.

3.5.2 Description of the comparator(s)

See Table 5 for an overview of teclistamab.

Table 5. Summary of teclistamab

Regimen	Generic names	ATC code	MoA	Form	Admini-stration	Dosing	Posology	Package Source size
Tecvayli	Teclistamab	L01FX24	bSAb	Solution injection	forSC	1.5 mg/m²	The recommended dosage of teclistamab is 1.5 mg/kg actual body weight1 administered once weekly after completion of the step-up dosing schedule. Step-up dose 1: 0.06 mg/kg, the first day of treatment; step-up dose 2: 0.3 mg/kg, two to four days after step-up dose 1; step-up dose 3: 1.5 mg/kg, two to four days after step-up dose 2. Additionally, in patients who have a complete response or better for a minimum of six months, a reduced dosing frequency of 1.5 mg/kg SC every two weeks may be considered (EMA 2023c).	

Abbreviations: BsAb, bi-specific antibody

3.6 Cost-effectiveness of the comparator(s)

Teclistamab was reimbursed by DMC on February 21st (2024) and is therefore considered cost-effective for the patient population at hand, triple-class exposed patients who have received at least three prior therapies (Medicinrådet 2024). Teclistamab achieved the status of cost-effective in part because The Medicine Council accounted for reduced dosing frequency for some patients, from administration every week to administration every other week. A reduction in dosing frequency for some, mainly those who achieved sustained complete response for at least six months, patients treated with teclistamab was considered in the current comparison between talquetamab and teclistamab.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The adjusted comparison allowed for the following efficacy outcomes: response rates (ORR, CR or better, VGPR or better), DOR, PFS, TTNT and OS. These outcomes are described and defined in Table 6 below. For all endpoints, participant follow-up began on the first day of treatment in both MonumenTAL-1 and MajesTEC-1. Data used in the analysis was based on MonumenTAL-1 data-cut of January 2023 (talquetamab 0.8 mg/kg Q2W median duration of follow-up: 12.7 months respectively) and MajesTEC-1 data-cut of January 2023 (median duration of follow-up: 22.8 months).

Table 6. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition & Validity	How was the measure investigated/method of data collection
Overall Response Rate (ORR)	See note below	ORR was defined as the proportion of participants who achieved a PR or better according to the IMWG criteria on the participant's assigned therapy. Validity: Adapted from IMWG criteria (Kumar et al. 2016)	ORR was adjudicated by the IRC for MonumenTAL-1 and MajesTEC-1
Complete Response or better rate (≥CR)	See note below	CR or better rate was defined as the percentage of participants achieving CR or sCR according to IMWG criteria Validity: Adapted from IMWG criteria (Kumar et al. 2016)	CR and sCR were adjudicated by the IRC for MonumenTAL-1 and MajesTEC-1.
Very Good Partial Response or better rate (≥VGPR)	See note below	VGPR or better rate was defined as the percentage of participants achieving VGPR or better according to IMWG criteria Validity: Adapted from IMWG criteria (Kumar et al. 2016)	VGPR or better rate was adjudicated by the IRC for MonumenTAL-1 and MajesTEC-1.
Duration of response (DOR)	See note below	DOR was defined as the time from initial documentation of a PR or better to the date of disease progression, or death due to any cause, whichever occurred first (Huang et al. 2018) Validity: Response defined by IMWG criteria (Kumar et al. 2016)	Participants who had not progressed and were alive at the data cut-off, were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy or at the last follow-up date, whichever occurred first.
Progression-Free Survival (PFS)	See note below	PFS was defined as the time from the index date to the date of progression or death due to any cause, whichever occurred first. Participants who had not progressed and were alive at the data cut-	PFS was adjudicated by the IRC for MonumenTAL-1 and MajesTEC-1.

Outcome measure	Time point*	Definition & Validity	How was the measure investigated/method of data collection
		off, were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy. Validity: PFS was evaluated according to IMWG criteria in both data sources (Kumar et al. 2016)	
Time to Next Treatment (TTNT)	See note below	TTNT was defined as the time from the index date to the initiation of the next therapy line or death due to any cause, whichever occurred first Validity: meaningful endpoint for patients with low grade, incurable malignancies (Delgado and Guddati 2021)	Participants who were still alive and did not initiate a next therapy line at time of data-cut were censored at last date known to be alive.
Overall Survival (OS)	See note below	OS was defined as the time from the index date to the date of the participant's death, due to any cause. Validity: gold standard primary clinical endpoint (Delgado and Guddati 2021)	Participants still alive or the vital status was unknown were censored at the date last known to be alive.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Time point of analysis: Data used in the analysis was based on MonumenTAL-1 data-cut of January 17 2023 (talquetamab 0.4 mg/kg Q1W and 0.8 mg/kg Q2W median duration of follow-up: 18.8 and 12.7 months respectively) and MajesTEC-1 data-cut of January 4 2023 (median duration of follow-up: 22.8 month)

Validity of outcomes

References related to validity of outcomes have been included in Table 6 above.

4. Health economic analysis

4.1 Model structure

A cost-effectiveness model (CEM) was developed to conduct a cost-effectiveness analysis for talquetamab to appropriately reflect the clinical trial evidence and patient pathway. The CEM was developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modelling Practices (Martin et al. 2020), and in keeping with the requirements of HTA bodies such as DMC and NICE (National Institute for Health and Care Excellence (NICE) 2019b).

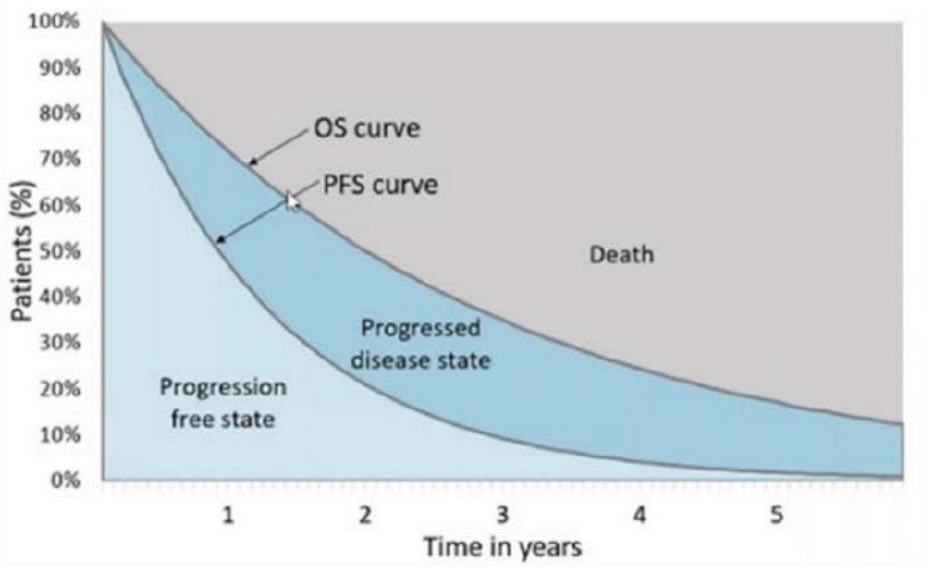
The CEM was fully programmed in Microsoft Excel and Visual Basic for Applications (VBA) was used to automate tasks such as conducting of sensitivity analyses and manipulating user interface features.

The outcomes of the CEM include total and incremental costs and health outcomes expressed both as life years (LYs) and QALYs gained. Therefore, the model can employ a cost-utility analysis calculating an incremental cost-effectiveness ratio (ICER) defined as the incremental costs per incremental QALYs gained. Mean and median PFS and OS are also presented, as well as disaggregated results showing the breakdown of LYs, QALYs, and costs per treatment arm.

The model structure uses a partitioned survival model (PSM) approach. The PSM includes three health states: progression-free (PF), post-progression (PD) and death. The PF state includes all patients who either have stable disease or respond to therapy. The PD state includes patients with progressive disease (PD, as defined in the clinical trial). It is assumed that all patients start in the PF state. From the PF health state, patients may transition to the other health states or remain in this health state at each model cycle. Following progression, patients are unable to transition back to the PF health state and can only transition to the ‘dead’ state, an absorbing health state, or stay in the post-progression state. At any time point in the model, a patient can be alive with non-progressed disease (progression-free), alive with progressed disease (post-progression) or dead.

In a PSM, OS and PFS are modelled independently and the proportion of patients in each health state over time are derived directly from the OS and PFS projections using an area under the curve approach (see Figure 3). The proportion of patients who are dead in each model cycle is estimated by one minus estimated survival, the proportion of those in the post-progression state is estimated by gap between OS and PFS projections, and the proportion in the progression-free state is the gap between the PFS projection and the x axis.

Figure 3. PSM Structure



Abbreviations: OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model

The PSM structure is both simple and flexible enough to extrapolate survival using various methods. It allows for key trial endpoints such as OS and PFS to be modelled directly, and reflects the clinical pathway of disease in that, once progressed, patients cannot return to the progression-free state. The approach is also representative of the clinical pathway for RRMM in that a patient's treatment course and outcomes will depend largely on whether their disease has progressed or remained progression free.

Utilities are applied to each health state. In PFS, patients receive the costs of drug acquisition, administration, co-medications, and treatment monitoring. For all treatment arms, AE costs are captured, and routine medical resource use is assigned by health state. Subsequent treatment costs are applied upon disease progression.

As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data are summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between comparators at model completion.

4.2 Model features

Table 7. Features of the economic model

Model features	Description	Justification
Patient population	Age (SD): 63.90 (9.62) Proportion female: 41.8% Body weight, mean (SD): 75.02 (16.73) Body surface area, mean (SD): 1.83 (0.242)	The population in the model is in line with the expected marketing authorisation, though based on MajesTEC-1 baseline characteristics (SOC) rather than the corresponding characteristics from MonumenTAL-1, encompassing adult patients with RRMM, who had three or more prior LOTs and have previously received a PI, IMiD, and anti-CD38 therapy; talquetamab (based on

Model features	Description	Justification
		MonumenTAL-1) has the same indication as teclistamab (based on MajesTEC-1).
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	35 years in the base case	A lifetime horizon up until max 100 years of age was selected in the base case because RRMM treatments have an impact on costs and outcomes over a patient's lifetime. The time horizon captures all health benefits and costs in line with DMC guidelines.
Cycle length	One week	Consistent with length of treatment cycle (7 days).
Half-cycle correction	Applied	A half-cycle correction is applied, to account for the transition of patients from one health state to another happening in a continuous process, representing an average transition of halfway through a cycle (i.e., not at the beginning or end of a cycle).
Discount rate	3.5% year 1–35	According to methods guide
Intervention	Talquetamab 0.8 mg/kg Q2W	Q2W dosing is the expected use in clinical practice according to internal Janssen Medical Advisor
Comparator	Teclistamab	Reimbursed by DMC for the same patient population as Talquetamab is being evaluated for.
Outcomes	OS, PFS, LYs and QALYs gained	

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was not the basis for choice of comparative effectiveness and safety in this analysis. Janssen is the market authorization holder of teclistamab, in addition to talquetamab, and has therefore full knowledge of its pivotal trials. MajesTEC-1 is the only pivotal trial for teclistamab in treatment of triple-class exposed patients who have received at least three prior treatments. Additionally, regardless of indication, MajesTEC-1 is to date the only clinical trial based on which teclistamab has been granted market authorization within the European Union (European Commission 2024).

Table 8. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Dose Escalation Study of Talquetamab in Participants with Relapsed or Refractory Multiple Myeloma (ClinicalTrials.gov 2017) A study of talquetamab in participants with Relapsed or Refractory multiple myeloma (ClinicalTrials.gov 2021) MonumenTAL-1 17 January 2023 data-cut CSR (Janssen 2023e)	MonumenTAL-1	NCT03399799, NCT04634552	Start: February 2021 Completion: April 2026 (estimated) Data cut-off: January 2023 Final data cut-off: November 2024	Talquetamab versus teclistamab for treatment of adult RRMM patients who are triple-class exposed

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Dose Escalation Study of teclistamab in Participants with Relapsed or Refractory Multiple Myeloma (ClinicalTrials.gov 2024a) A study of teclistamab in participants with Relapsed or Refractory Multiple Myeloma (ClinicalTrials.gov 2024b) MajesTEC 4 January 2023 data-cut CSR (Janssen 2023c)	MajesTEC-1	NCT03145181, NCT04557098	Start: May 2017 Completion: September 2025 (estimated) Data cut-off: January 2023 Final data cut-off: August 2023*	Talquetamab versus teclistamab for treatment of adult RRMM patients who are triple-class exposed

Abbreviations: RRMM, Relapsed and/or Refractory Multiple Myeloma;

5.2 Literature used for the assessment of health-related quality of life

Not applicable. Health-related quality of life data were obtained from the two relevant pivotal studies, MonumenTAL-1 and MajesTEC-1.

5.3 Literature used for inputs for the health economic model

Literature has been used to inform disutilities of adverse events, which are described in section 0. No other literature has been used to inform the health economic model.

Table 9. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Bacelar, M., Cooper, C., Hyde, C., Latimer, N. & Murray, D. 2014. The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171). Single Technology Appraisal NIHR HTA Programme (13/07/01). Matrix and Peninsula Technology Assessment Group 2014. [Online]. Available: https://www.nice.org.uk/guidance/gid-tag452/documents/multiple-myeloma-lenalidomide-post-bortezomib-part-rev-ta171-evaluation-report2 [Accessed 5 October 2023]. (Bacelar et al. 2014)	Disutility of adverse events, incl. aPTT increased, AST increased, Gamma-glutamyltransferase increased, Leukopenia, Lymphopenia, Neutropenia, Pneumonia, Pyrexia	TLR	Section 0
Ossa, D. F., Briggs, A., Mcintosh, E., Cowell, W., Littlewood, T. & Sculpher, M. 2007. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. Pharmacoeconomics, 25, 223-37. (Ossa et al. 2007)	Disutility of adverse events, incl. Anemia, and Thrombocytopenia	TLR	Section 0
Lloyd, A., Nafees, B., Narewska, J., Dewilde, S. & Watkins, J. 2006. Health state utilities for metastatic breast cancer. Br J Cancer, 95, 683-90. (Lloyd et al. 2006)	Disutility of adverse events, incl. Asthenia and fatigue, and Diarrhea	TLR	Section 0
Hettle, R., Corbett, M., Hinde, S., Hodgson, R., Jones-Diette, J., Woolacott, N. & Palmer, S. 2017. The assessment and appraisal of regenerative medicines and cell therapy products: an	Disutility of adverse events, incl. CRS, Grade 3+	TLR	Section 0

exploration of methods for review, economic evaluation and appraisal. Health Technol Assess, 21, 1-204. (Hettle et al. 2017)			
Launois, R., Reboul-Marty, J., Henry, B. & Bonneterre, J. 1996. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. Pharmacoeconomics, 10, 504-21. (Launois et al. 1996)	Disutility of adverse events, incl. Febrile neutropenia	TLR	Section 0
Smith-Palmer, J., Bae, J. P., Boye, K. S., Norrbacka, K., Hunt, B. & Valentine, W. J. 2016. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res, 8, 559-571. (Smith-Palmer et al. 2016)	Disutility of adverse events, incl. Hyperglycemia	TLR	Section 0
NICE appraisal TA573 (Table 46 Committee papers) National Institute for Health and Care Excellence (Nice). 2023. Single Technology Appraisal Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057] Committee Papers [Online]. Available: https://www.nice.org.uk/guidance/ta897/history [Accessed 27 March 2024] (National Institute for Health and Care Excellence (NICE) 2023)	Disutility of adverse events, incl. Hypertension	TLR	Section 0
NICE appraisal TA510 of daratumumab 2019 (Table 60 Appraisal consultation committee papers) National Institute for Health and Care Excellence (Nice). 2018. Single Technology Appraisal daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933] Committee Papers [Online]. Available: https://www.nice.org.uk/guidance/ta783/evidence [Accessed 27 March 2024]. (National Institute for Health and Care Excellence (NICE) 2018)	Disutility of adverse events, incl. Hypokalemia	TLR	Section 0
Tolley, K., Goad, C., Yi, Y., Maroudas, P., Haiderali, A. & Thompson, G. 2013. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ, 14, 749-59. (Tolley et al. 2013)	Disutility of adverse events, incl. Sepsis	TLR	Section 0

Abbreviations: TLR: Targeted literature review

6. Efficacy

6.1 Efficacy of talquetamab compared to teclistamab for triple-exposed RRMM

6.1.1 Relevant studies

Given the absence of a comparator arm in MonumenTAL-1, an external control arm was used to assess comparative effectiveness of talquetamab versus teclistamab.

The pivotal study investigating talquetamab is the MonumenTAL-1 study (NCT03399799, NCT04634552). Hence, MonumenTAL-1 provides the basis for the efficacy and safety evidence for talquetamab in this assessment.

The pivotal study investigating teclistamab, in the same patient population as MonumenTAL-1, is the MajesTEC-1 study (NCT03145181, NCT04557098). Hence, MajesTEC-1 provides the basis for the efficacy and safety evidence for teclistamab in this assessment (see further section 7 and Appendix A).

A systematic literature review (SLR) was not the basis for choice of comparative effectiveness in this analysis, as such the most relevant documentation for efficacy and safety (intervention and comparator) were determined to be the above-mentioned studies.

6.1.1.1 MonumenTAL-1 (NCT03399799, NCT04634552)

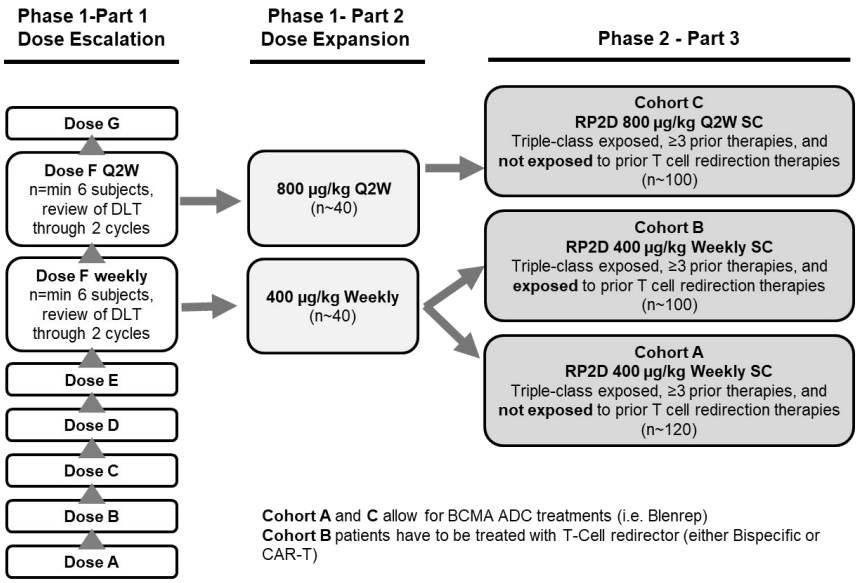
MomumenTAL-1 is an ongoing, first-in-human, Phase 1/2, open-label, multicenter clinical trial evaluating the safety, tolerability, pharmacokinetics, and anti-myeloma activity of talquetamab in the treatment of adult patients with triple-class exposed (TCE) RRMM (see Appendix A Table 47. for patient eligibility) (Janssen 2023e).

The study was conducted in three parts (see Figure 4):

- Part 1 (dose escalation; Phase 1): to characterize the safety of talquetamab and to identify the recommended Phase 2 doses (RP2Ds).
- Part 2 (dose expansion; Phase 1): to further characterize the safety of talquetamab at the putative RP2Ds.
- Part 3 (dose expansion; Phase 2): to evaluate the efficacy of talquetamab at the RP2Ds in cohorts of TCE patients with RRMM who previously received ≥3 prior lines of therapy (LOT).
    - The efficacy and safety results from the Phase 2 study are presented in Section 6.1.4 and Appendix B Section B.1 (efficacy) and Section 9.1 and Appendix E (safety) for patients with no prior exposure to T cell redirection therapy (eg,

bispecific antibodies and chimeric antigen receptor T cell therapy [CAR-T])[1]. Outcomes for Cohort B, which included patients who previously received T cell redirection therapy, are not reported in this application.

Figure 4. Overall study design, MonumenTAL-1



Note: The Q1W SC RP2D in Phase 1 was 405 µg/kg; this changed to 400 µg/kg in Phase 2 for operational convenience, with similar exposure. Both Q1W SC RP2Ds are shown as 0.4 mg/kg in the primary CSR.

Abbreviations: ADC = antibody-drug conjugate; BCMA = B-cell maturation antigen; Blenrep = belantamab mafodotin; CAR-T = chimeric antigen receptor T-cell therapy; DLT = dose-limiting toxicity; Q1W = weekly; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneously.

Source: (Janssen 2022e).

A wide range of escalating dose levels of talquetamab, administered either intravenously (IV; 0.0005 mg/kg Q2W up to 0.18 mg/kg Q1W) or subcutaneously (SC; 0.0015 mg/kg Q1W up to 1.6 mg/kg monthly), were evaluated in Part 1 of the study (Janssen 2022e). Based on pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data from Parts 1 and 2, the RP2Ds of 0.4 mg/kg SC Q1W2 (preceded by step up doses of 0.01 and 0.06 mg/kg) and 0.8 mg/kg SC Q2W (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg) were selected to further evaluate the safety and efficacy of talquetamab in Part 3 of the study. In all parts of the study, patients continued to receive talquetamab until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study. The end of study was defined as 2 years after the last patient had received the initial dose of talquetamab or when the last patient had completed the last study assessment in the study, whichever occurred first.

The clinical cutoff date for the MonumenTAL-1 data presented in this report was January 2023. The median duration of follow-up was 12.7 months (range: 0.2 to 26.1 months) for Cohort C. Patient enrolment[3] was initiated in March 2021 based on phase 1 part 2 of MonumenTAL-1 (dose

[1] Cohort C allowed for patients to have prior exposure to B-cell maturation antigen (BCMA)-directed antigen-drug conjugates (ADC), such as belantamab mafodotin.

[2] Adjusted from the RP2D of 0.405 mg/kg for operational convenience, with similar exposure to talquetamab. In the primary CSR, "0.4 mg/kg Q1W SC" referred to results for both the Phase 1 dose (0.405 mg/kg Q1W SC) and the Phase 2 dose (0.4 mg/kg Q1W SC).

[3] Initiation of enrolment refers to the date of the first patient receiving his or her first dose of Talquetamab

expansion), while the corresponding date for the study's phase 2 part 3, was October 2021. Enrolment occurred across 45 sites, in the following areas: Europe (56.6%), North America (40.7%), and Asia (2.8%).

6.1.1.2 MajesTEC-1 (NCT03145181, NCT04557098)

The clinical development program for teclistamab in RRMM includes MajesTEC-1, a pivotal clinical trial assessing the efficacy and safety of teclistamab as a monotherapy ([NCT03145181/ NCT04557098], Phase 1/2). MajesTEC-1 is an ongoing, first-in-human, Phase 1/2, open label, multicenter clinical trial in adults with RRMM that had received at least three prior lines of therapy and had received a PI, an IMiD and an anti-CD38 mAb in any order during the course of treatment. The phase 1 portion assessed dose escalation and expansion of teclistamab, while the phase 2 portion examines efficacy. The study is currently ongoing.

The study included three cohorts:

- Cohort A: included patients with ≥3 prior MM treatment LOT and previously received an IMiD, PI, and anti-CD38 mAb
- Cohort B: was initially planned to enroll patients who were more heavily pre-treated (≥four prior LOT) and considered penta-drug refractory (i.e., refractory to >2 PIs, >2 IMiDs, and an anti-CD38 mAb). However, Cohort B was not opened for enrolment as penta-drug refractory patients were enrolled in Cohort A.
- Cohort C included patients with ≥3 prior lines of treatment that included a PI, an IMiD, an anti-CD38 mAb, and an anti-BCMA treatment (with CART-T cells or an antibody drug conjugate).

A total of 165 subjects (40 in Phase 1 and 125 in Cohort A in Phase 2) received at least 1 dose of teclistamab at recommended phase 2 dose (RP2D; 1.5 mg/kg) on or before the clinical cut-off date of January 4th, 2023, and were included in the All Treated Analysis Set, the relevant population for this assessment. The median follow-up was 22.8 months (range: 0.3 [subject died] to 33.6 months and the 165 subjects in the All Treated Analysis Set received a median of 9.3 months of therapy (range: 0.2 to 33.6).

As of the clinical cut-off 4th of January 2023, 47 subjects remain on treatment and the majority of these (n=42 [89.4%]) are receiving dosing every second week (Q2W) or once per month (Q4W). For further details on MajesTEC-1 study design, key inclusion and exclusion criteria as well as study end points are described in detail in Appendix A.

Table 10. Overview of study design for studies included in the comparison

	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
MonumenTAL-1 NCT03399799, NCT04634552 (ClinicalTrials.gov 2017) (ClinicalTrials.gov 2021) (Janssen 2022e)	Phase 1/2, open-label, multicenter single arm clinical trial	Clinical cutoff date: January 2023 Median follow-up: 12.7 months for Cohort C	Adult relapsed or refractory MM patients who have previously received ≥3 prior lines of therapy that included at least a PI, an IMiD, and an anti-CD38 monoclonal antibody* *The study consisted of three cohorts (A, B and C). Cohort B in addition were exposed to T cell redirection therapies such as CAR-T cells or bispecific	Cohort C: talquetamab 0.8 mg/kg Q2W SC (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg)	N/A	Primary endpoint: • Overall Response Rate (ORR) Secondary endpoints: • Duration of Response (DOR) • Very Good Partial Response (VGPR) or Better Rate • Complete Response (CR) or Better Rate • Stringent Complete Response (sCR) Rate • Time to Response (TTR) • Progression-free Survival (PFS) • Overall survival (OS) • Minimal Residual Disease (MRD) Negative Rate • Number of Participants with Adverse Events (AEs) as a Measure of Safety and Tolerability • Number of Participants with Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability • Number of Participants with AEs by Severity • Number of Participants with Abnormalities in Clinical Laboratory Values • Serum Concentration of Talquetamab • Number of Participants with Talquetamab Antibodies • Change from Baseline in Health-Related Quality of Life (HRQoL) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) • Change from Baseline in HRQoL as Assessed by EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L)

	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			antibodies. This cohort is not included in the analysis.			• Change from Baseline in HRQoL as Assessed by Patient Global Impression of Severity (PGIS) • Overall Response Rate (ORR) in Participants with High-risk Molecular Features Median follow-up (17 January 2023 data-cut): 12.7 months for cohort C
MajesTEC-1 NCT03145181, NCT04557098 (ClinicalTrials.gov 2024a) (ClinicalTrials.gov 2024b) (Janssen 2023c)	Phase 1/2, open-label, multicenter single arm clinical trial	Clinical cutoff date: 4 January 2023 Median follow up duration: 22.8 months	Adult relapsed or refractory MM patients who have previously received ≥3 prior lines of therapy that included at least a PI, an IMiD, and an anti-CD38 monoclonal antibody	Teclistamab 1.5 mg/kg weekly SC (preceded by step-up doses of 0.06 mg/kg, 0.3 mg/kg, and 1.5 mg/kg). In patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg SC every two weeks may be considered	N/A	Primary endpoint: • Overall Response Rate (ORR) Secondary endpoints: • Duration of Response (DOR) • Very Good Partial Response (VGPR) or Better Rate • Complete Response (CR) or Better Rate • Stringent Complete Response (sCR) Rate • Time to Response (TTR) • Clinical Benefit Rate (CBR) • Duration of Response (DOR) • Time to Response (TTR) • Progression-free Survival (PFS) • Overall survival (OS) • Minimal Residual Disease (MRD) Negative Rate • Number of Participants with Adverse Events (AEs) as a Measure of Safety and Tolerability • Number of Participants with Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability • Number of Participants with AEs by Severity • Number of Participants with Abnormalities in Clinical Laboratory Values

	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• Serum Concentration of teclistamab • Number of Participants with teclistamab Antibodies • Change from Baseline in Health-Related Quality of Life (HRQoL) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) • Change from Baseline in HRQoL as Assessed by EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L) • Change from Baseline in HRQoL as Assessed by Patient Global Impression of Severity (PGIS) • Overall Response Rate (ORR) in Participants with High-risk Molecular Features Median follow-up (4 January 2023 data-cut): 22.8 months

Abbreviations: AE, Adverse Event; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CBR, Clinical Benefit Rate; CD38, Cluster of Differentiation 38; CR, Complete Response; DOR, Duration of Response; EORTC QLQ, European Organizatio for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol Five Dimension Five Level Questionnaire, Five Dimension, Five Level; HRQoL, Health Related Quality of Life; IMID, Immunomodulatory Drug; MM, Multiple Myeloma; MRD, Minimal Residual Disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-free Survival; PFS2, Time to progression on the next line of subsequent antimyeloma therapy or death; PGIS, Patient Global Impression of Severity; PI, Proteasome Inhibitor;; SAE, Serious Adverse Event; SC, Subcutaneous; sCR, Stringent Complete Response; SOC, Standard of Care; TTNT, Time to Next Treatment; TTR, Time To Response; VGPR, Very Good Partial Response.

6.1.2 Comparability of studies

In the present study, adjusted comparisons using IPTW methods to adjust for differences in clinically important prognostic patient characteristics at baseline were used to compare the effectiveness of talquetamab versus teclistamab in triple-class exposed patients with relapsed or refractory multiple myeloma (Li et al. 2018, Rosenbaum and Rubin 1983).

Key inclusion/exclusion criteria from MonumenTAL-1 are outlined below, whilst the full eligibility criteria for the MonumenTAL-1 study are outlined in Appendix A Table 47. The full eligibility criteria for the MajesTEC-1 studies are outlined in Appendix A Table 48. As previously mentioned, the inclusion and exclusion criteria of MonumenTAL-1 and MajesTEC-1 are comparable.

- Adults (≥18 years of age) with relapsed or refractory multiple myeloma
- Measurable disease as defined by IMWG consensus criteria
- Received at least 3 prior lines of antimyeloma therapy
    - Clarification 1: Induction with or without HSCT and with or without maintenance therapy is considered a single line of therapy.
    - Clarification 2: To count as a line of therapy, a single antimyeloma agent or regimen must be given for at least 1 complete cycle of treatment, unless PD was the best response for that line.
- Received as part of previous therapy a PI, an IMiD, and an anti-CD38 monoclonal antibody (prior exposure can be from different monotherapy or combination lines of therapy)
- Have documented evidence of progressive disease based on investigator's determination of response by IMWG criteria on or within 12 months of their last line of therapy. Participants with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are also eligible.
- Have an ECOG performance status score of 0 to 2
- Adequate bone marrow reserve, defined as haemoglobin ≥8.0 g/dL
- Adequate renal function, defined as creatinine clearance ≥40 mL/min/1.73m^2
- Have not received prior T cell redirection therapy such as CAR-T cell therapy or bispecific antibodies

The adjusted comparison considered the following efficacy outcomes: ORR, CR or better rate, VGPR or better rate, DOR, PFS, TTNT, and OS. Definitions and schedule of assessment of these endpoints are provided in Table 6 which are similar for both MonumenTAL-1 and MajesTEC-1.

6.1.2.1 Schedule of Assessment

For all endpoints, participant follow-up began on the first day of treatment in both MonumenTAL-1 and MajesTEC-1. Outcome assessment schedules for MonumenTAL-1 and MajesTEC-1 included assessments for response and progression at each treatment cycle. To evaluate for the similarity in data collection timepoints for MonumenTAL-1

and MajesTEC-1, the timing between visits was assessed. Median days between visits was the same in both the MonumenTAL-1 study and the MajesTEC_1 study (28 days).

6.1.2.2 Comparability of patients across studies

For the MonumenTAL-1 cohort, the all-treated analysis set included a total of 145 participants in the 0.8 mg/kg Q2W SC cohort. The 0.8 mg/kg Q2W cohort consisted of participants treated with talquetamab in Cohort C, and participants from Phase 1 who received talquetamab at 0.8 mg/kg Q2W SC and were not previously exposed to T cell redirecting therapy.

The MajesTEC-1 cohort included a total of 165 patients, the entire ITT cohort.

Baseline prognostic factors considered for statistical adjustment were selected a priori based on feedback from Internal Janssen Medical Advisors. Adjusted comparisons were conducted using IPTW with ATC weighting in the main analyses. The main analysis adjusted for refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines of therapy, age, haemoglobin, LDH, creatinine clearance, ECOG score, sex, type of multiple myeloma, prior stem cell transplant, race, and cytogenetic profile. For full details of the weighting procedures, see Appendix C.

IPTW with ATC weighting was selected for the main analyses since IPTW with ATT weighting was applied in the Danish Medicines council's recent evaluation of teclistamab for treatment of triple-class exposed RRMM patients, based on the MajesTEC-1 study; the Danish Medicines council has thus recognized the MajesTEC-1 study population as a valid representation of Danish triple-class exposed RRMM patients (Medicinrådet 2024).

Table 11 (talquetamab 0.8 mg/kg Q2W) provides the participant numbers for both the MonumenTAL-1 and MajesTEC-1 cohort, for all baseline risk factors by categories, including SMD values as measure of balance, with SMD ≤0.20 indicating balance between both cohorts.

Table 11. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – Talquetamab 0.8 mg/kg Q2W

Talquetamab 0.8 mg/kg Q2W		Observed (Before ATT Weighting)			After ATC Weighting Main analysis		After ATT Weighting Sensitivity analysis	
		MonumenTAL-1 N (%) 143 (100%)	MajesTEC-1 N (%) 165 (100%)	SMD	MonumenTAL-1 Weighted N (%) 145 (100%)	SMD	MajesTEC-1 Weighted N (%) 165 (100%)	SMD
Refractory status[1]	≤ Double refractory[2]	45 (31.0)	37 (22.4)	0.268	[redacted]			
	Triple-class refractory[3]	24 (16.6)	20 (12.1)					
	Quad-class refractory[4]	41 (28.3)	58 (35.2)					
	Penta-class refractory[5]	35 (24.1)	50 (30.3)					
ISS stage	I	65 (44.8)	87 (52.7)	0.316				
	II	45 (31.0)	58 (35.2)					
	III	35 (24.1)	20 (12.1)					
Time to progression on last regimen	< 3 months	41 (28.3)	50 (30.3)	0.045				
	≥ 3 months	104 (71.7)	115 (69.7)					
Extramedullary plasmacytoma[6]	Yes	37 (25.5)	28 (17.0)	0.210				
	No	108 (74.5)	137 (83.0)					
Number of prior lines of therapy	≤ 4	69 (47.6)	78 (47.3)	0.006				
	> 4	76 (52.4)	87 (52.7)					

Talquetamab 0.8 mg/kg Q2W		Observed (Before ATT Weighting)			After ATC Weighting Main analysis		After ATT Weighting Sensitivity analysis	
		MonumenTAL-1 N (%) 143 (100%)	MajesTEC-1 N (%) 165 (100%)	SMD	MonumenTAL-1 Weighted N (%) 145 (100%)	SMD	MajesTEC-1 Weighted N (%) 165 (100%)	SMD
Years since multiple myeloma diagnosis	< 6 ≥ 6	67 (46.2) 78 (53.8)	81 (49.1) 84 (50.9)	0.058	[redacted]			
Average duration of prior lines (months)	< 10 10-14 ≥ 15	37 (25.5) 35 (24.1) 73 (50.3)	41 (24.8) 51 (30.9) 73 (44.2)	0.158				
Age	< 65 ≥ 65	63 (43.4) 82 (56.6)	86 (52.1) 79 (47.9)	0.174				
Hemoglobin (g/dL)	< 12 ≥ 12	113 (77.9) 32 (22.1)	124 (75.2) 41 (24.8)	0.066				
LDH levels (units/L)	< 280 ≥ 280	111 (76.6) 34 (23.4)	123 (74.5) 42 (25.5)	0.047				
Creatinine clearance	<60 60 to <90 ≥ 90	45 (31.0) 68 (46.9) 32 (22.1)	44 (26.7) 73 (44.2) 48 (29.1)	0.166				
ECOG status	0 1-2	56 (38.6) 89 (61.4)	55 (33.3) 110 (66.7)	0.110				
Sex	Male Female	83 (57.2) 62 (42.8)	96 (58.2) 69 (41.8)	0.019				
Type of multiple myeloma	IgG Non-IgG	77 (53.1) 68 (46.9)	91 (55.2) 74 (44.8)	0.041				

Talquetamab 0.8 mg/kg Q2W		Observed (Before ATT Weighting)			After ATC Weighting Main analysis		After ATT Weighting Sensitivity analysis	
		MonumenTAL-1 N (%) 143 (100%)	MajesTEC-1 N (%) 165 (100%)	SMD	MonumenTAL-1 Weighted N (%) 145 (100%)	SMD	MajesTEC-1 Weighted N (%) 165 (100%)	SMD
Prior stem cell transplant	Yes	114 (78.6)	135 (81.8)	0.080	[redacted]			
	No	31 (21.4)	30 (18.2)					
Race[7]	White	125 (86.2)	134 (81.2)	0.136				
	Other/Not Reported	20 (13.8)	31 (18.8)					
Cytogenetic profile	Standard Risk	91 (62.8)	110 (66.7)	0.082				
	High Risk[7]	37 (25.5)	38 (23.0)					
	Missing	17 (11.7)	17 (10.3)					
[redacted]								

Abbreviations: ATT, average treatment effect in the treated; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IMID, immunomodulatory drug; ISS, International Staging System; LDH, lactate dehydrogenase; NOBS, number of observations; PI, proteasome inhibitor; Q2W, once every 2 weeks; SC, subcutaneous; SMD, standardized mean difference

The pre-weighting and post-weighting distributions of demographics by intervention group are shown. SMDs >0.2 are considered to indicate important differences between groups. Main analysis adjusted for refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines of therapy, age, haemoglobin level, LDH level, creatinine clearance, ECOG status, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables adjusted for all variables in the main analysis, plus race and cytogenetic profile.

[1] Refractoriness was defined by International Myeloma Working Group consensus criteria (MonumenTAL-1).

[2] Refractory status of less than triple refractory; [3] Refractory to 1 IMiD, 1 PI, and 1 anti-CD38 monoclonal antibody; [4] Refractory to ≥2 IMiDs, 1 PI, and 1 anti-CD38 monoclonal antibody or ≥2 PIs, 1 IMiD, and 1 anti-CD38 monoclonal antibody; [5] Refractory to ≥2 IMiDs, ≥2 PIs, and 1 anti-CD38 monoclonal antibody; [6] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas.(Caers et al. 2018); [7] At least 1 of del17p. t(14;16). or t(4;14).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The MonumenTAL-1 study population, and the MajesTEC-1 study population, were assessed to be comparable with the Danish patients eligible for treatment. The target patient population for this assessment consist of adult Danish patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including IMiD, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy and is in line with the expected indication of talquetamab. Key patient characteristics and efficacy was based on MajesTEC-1, the pivotal clinical trial for teclistamab, which correspond well to Danish patients with triple-class exposed RRMM (Janssen 2023b); baseline characteristics from MajesTEC-1 was selected ahead of the corresponding characteristics from MonumenTAL-1, since the base case indirect treatment comparison was carried out in the MajesTEC-1 population.

Some baseline characteristics of patients with newly diagnosed MM are described in the treatment guidelines from the DMC (Medicinrådet 2020). They generally agree with baseline characteristics from the MajesTEC-1 (and MonumenTAL-1) study, the major difference being the median age of 71 years in the DMC guidance vs 64 years in MajesTEC-1. It should however be noted that the DMC guideline describes a patient population initiating 1st line treatment, whereas patients eligible to teclistamab (and talquetamab) can be expected to have an earlier onset of disease. Thus, because of lack of data in 4th line Danish population, characteristics from MajesTEC-1 were used in the health economic model.

Table 12. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (MajesTEC-1)
Age	71 (Medicinrådet 2020)	63.90
Gender	50% female (Medicinrådet 2020)	41.8% female
Patient weight	73.4 kg (Medicinrådet 2020)	75.02 kg
BSA	1.84 m^2 (Medicinrådet 2020)	1.83 m^2

Abbreviations: BSA, body surface area.

6.1.4 Efficacy – results per MonumenTAL-1

6.1.4.1 Efficacy overview

At the time of the clinical cut-off of January 17, 2023, the all-treated analysis set included 145 patients (Phase 1: 36; Phase 2 Cohort C: 109) who were treated with talquetamab at the RP2D of 0.8 mg/kg Q2W SC. Mean duration of follow-up was 12.7 months (range: 0.2 to 26.1 months). Median treatment duration of Talquetamab treatment was 8.8 months (range: <0.1 to 25.7). At the clinical cut-off 58.6% (Cohort C) had discontinued talquetamab treatment, most frequently due to progressive disease (34.5%). For Cohort C, 41 patients (28.3%) discontinued study participation (32 [22.1%] died [1 due to COVID-19], 5 [3.4%] withdrew consent, and 1 [0.7%] was lost to follow-up) and 85 patients (58.6%) discontinued talquetamab (50 [34.5%] due to PD, 12 [8.3%] due to an AE, 12 [8.3%] due to physician decision, 6 [4.1%] refused treatment, and 5 [3.4%] died).

Table 14 gives an overview of the efficacy results for some of the main outcomes in MonumenTAL-1 for the all-treated population. The median PFS was 14.2 months . Median OS was not reached. The Kaplan-Meier curves for PFS are presented in Figure 5 and Kaplan-Meier curves for OS are presented in Figure 6. The ORR was >70% , with approximately 60% of patients achieving VGPR or better.

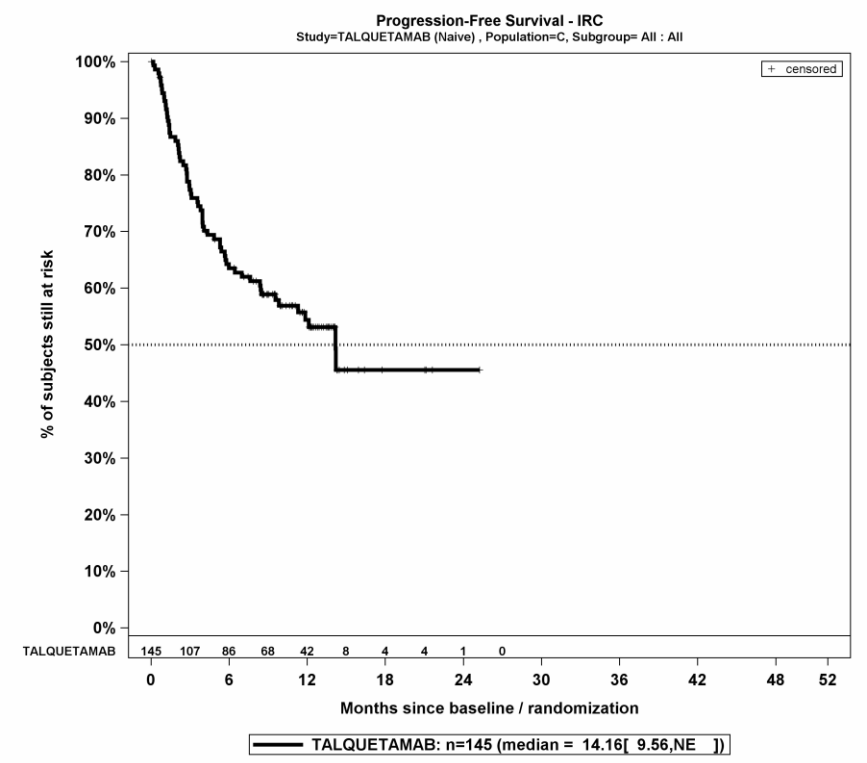
Table 13. Overview of MonumenTAL-1 efficacy results for Talquetamab, January 17 2023 cut-off

Outcome	Talquetamab 0.8 mg/kg Q2W (n=145)	95% CI
Progression-free survival, median (months)	14.2	9.6, NE
6-month progression free survival rate	63.5%	54.9%, 70.9%
9-month progression free survival rate	58.9%	50.2%, 66.6%
12-month progression free survival rate	54.4%	45.3%, 62.6%
Overall survival, median (months)	NE	20.1, NE
6-month overall survival rate	85.2%	78.2%, 90.1%
9-month overall survival rate	83.0%	75.8%, 88.3%
12-month overall survival rate	77.4%	69.1%, 83.7%
ORR (sCR + CR + VGPR + PR) n (%)	104 (71.7%)	63.7%, 78.9%
sCR	43 (29.7%)	22.4%, 37.8%
CR	13 (9.0%)	4.9%, 14.8%
VGPR	32 (22.1%)	15.6%, 29.7%
PR	16 (11.0%)	6.4%, 17.3%
MR	0	NE, NE
SD	27 (18.6%)	12.6%, 25.9%
PD	9 (6.2%)	2.9%, 11.5%

Note: Progression free survival and response based on response review committee assessment.
Abbreviations: sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; MR= minimal response; ORR = overall response rate; SD = stable disease; PD = progressive disease.

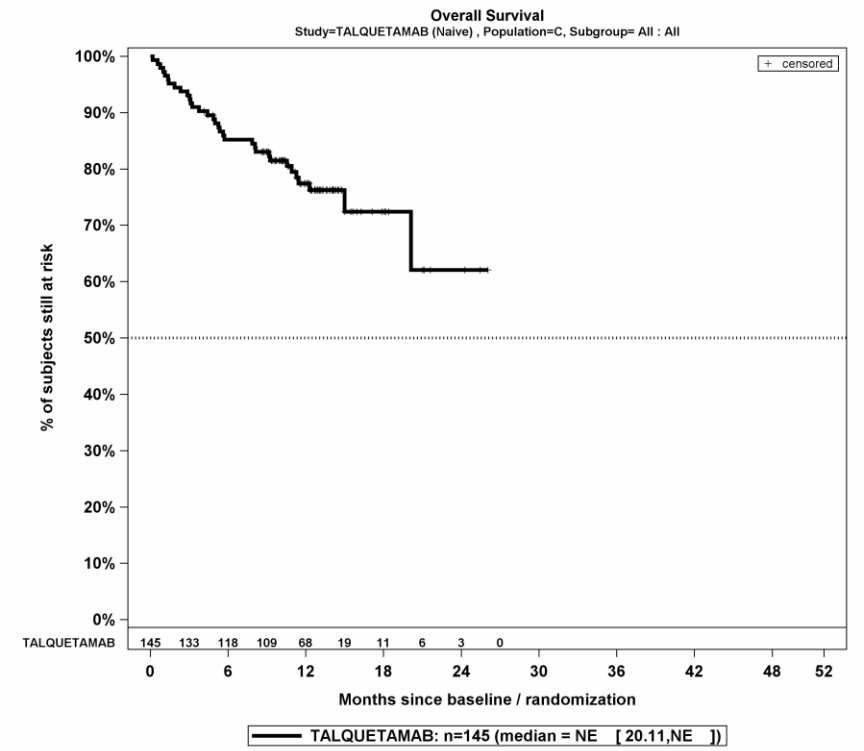
Source: (Janssen 2023e)

Figure 5. Kaplan–Meier plot for PFS to talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)



Note: Progressive disease was assessed by IRC, based on IMWG consensus criteria (2016).
Abbreviations: IMWG = International Myeloma Working Group; IRC = independent review committee; PFS = progression-free survival; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Source: (Janssen 2023e).

Figure 6. Kaplan–Meier plot for OS to talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)



Abbreviations: OS = overall survival; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Source: (Janssen 2023e).

6.1.4.2 Safety

Safety data from the MonumenTAL-1 study are presented in section 9.1 and Appendix E.

6.1.5 Efficacy – results per MajesTEC-1

6.1.5.1 Efficacy overview

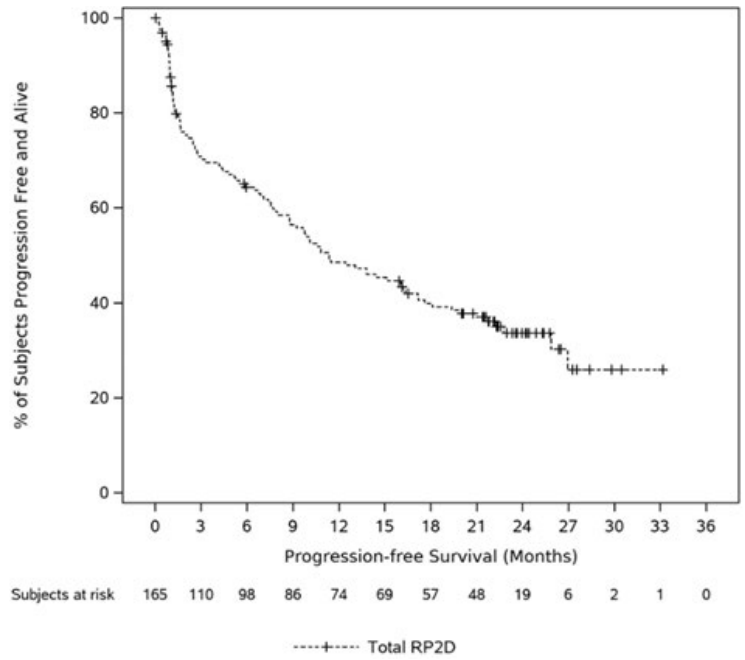
At the time of the clinical cut-off of January 4, 2023, the all-treated analysis set included 165 patients (Phase 1: 40; Phase 2 Cohort A: 125 who were treated with teclistamab at the RP2D of 1.5 mg/kg Q1W SC. Mean duration of follow-up was 22.8 months (range: 0.3 to 33.6 months). Median treatment duration of Teclistamab treatment was 9.3 months (range: 0.2 to 33.6). At the clinical cut-off, 71.5% had discontinued Teclistamab treatment, most frequently due to progressive disease (42.4%), while 90 patients had discontinued study participation, the majority because of death (83 patients) but seven withdrew consent. Table 14 gives an overview of the efficacy results for some of the main outcomes in MajesTEC-1 for the all-treated population. The median PFS was 11.3 months (95% CI: 8.8, 16.4). The 12-month PFS rate was 48.6% (95% CI: 40.5%, 56.2%). The median time for OS was 21.9 months (95% CI: 15.1, NE). The 12-month OS rate was 64.0% (95% CI: 56.0%, 70.9%). The Kaplan-Meier curves for PFS and OS are presented in Figure 7 and Figure 8 respectively. The ORR was 63%, with 59% of patients achieving VGPR or better.

Table 14. Overview of MajesTEC-1 efficacy results for Teclistamab January 2023 cut-off

Outcome	Teclistamab	95% CI
Progression-free survival, IRC assessment, median (months)	11.3	8.8, 16.4
6-month progression free survival rate	64.4%	56.4%, 71.3%
12-month progression free survival rate	48.6%	40.5%, 56.2%
18-month progression free survival rate	39.9%	32.1%, 47.5%
24-month progression free survival rate	33.7%	25.9%, 41.6%
Overall survival, median (months)	21.9	15.1, NE
6-month overall survival rate	77.8%	70.6%, 83.4%
12-month overall survival rate	64.0%	56.0%, 80.7%
18-month overall survival rate	54.5%	46.4%, 61.8%
24-month overall survival rate	48.7%	40.5%, 56.3%
Overall response (sCR + CR + VGPR + PR) n (%)	104 (63.0%)	55.2%, 70.4%
sCR	62 (37.6%)	30.2%, 45.4%
CR	13 (7.9%)	4.3%, 13.1%
VGPR	23 (13.9%)	9.0%, 20.2%
PR	6 (3.6%)	1.3%, 7.7%
MR	2 (1.2%)	0.1%, 4.3%
SD	28 (17.0%)	11.6%, 23.6%
PD	(17.3%)	9.0%, 20.2%
NE	8 (4.8%)	2.1%, 9.3%

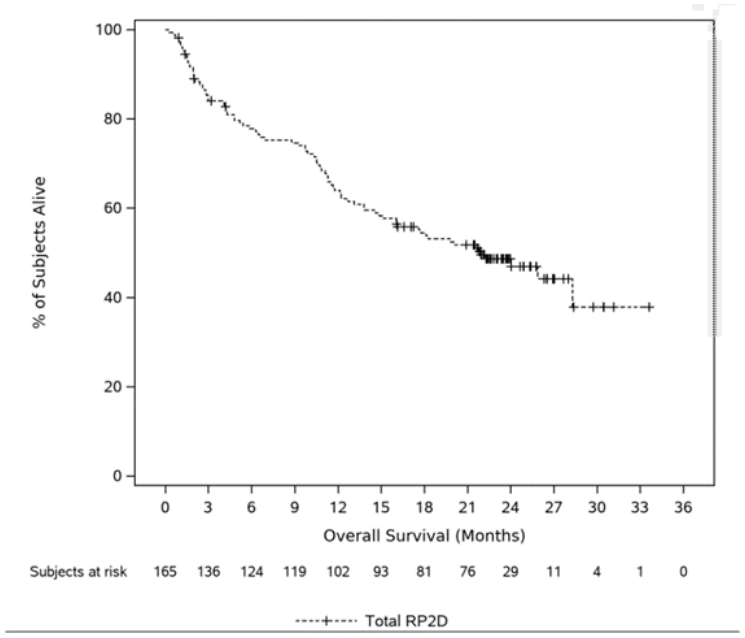
Note: Progression free survival and response based on independent review committee assessment.
Abbreviations: sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; MR= minimal response; IRC=Independent Review Committee; SD = stable disease; PD = progressive disease; NE = Not evaluable .
Source: (Janssen 2023c).

Figure 7. Kaplan-Meier curve for progression-free survival MajesTEC-1, January 2023 data cut



Abbreviations: RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group. Note: Progressive disease was assessed by IRC, based on IMWG consensus criteria (2016).
Source: (Janssen 2023c)

Figure 8. Kaplan-Meier curve for overall survival MajesTEC-1, January 2023 data cut



Abbreviations: RP2D = recommended Phase 2 dose.
Source: (Janssen 2023c)

6.1.5.2 Safety

Safety data from the MajesTEC-1 study are presented in section 9.1 and Appendix E.

7. Comparative analyses of efficacy

Comparative efficacy of talquetamab has not been assessed in any head-to-head clinical studies in patients with triple-class exposed relapsed or refractory multiple myeloma. In the absence of head-to-head studies, an external control arm and adjusted comparisons using IPTW methods was used to assess comparative effectiveness of talquetamab versus teclistamab. As previously presented, the efficacy and safety of the former was based on the MonumenTAL-1 study, while the corresponding information of the latter was based on the MajesTEC-1 study.

7.1.1 Differences in definitions of outcomes between studies

For all endpoints, participant follow-up began on the first day of treatment in both MonumenTAL-1 and MajesTEC-1. Outcome assessment schedules for MonumenTAL-1 and MajesTEC-1 included assessments for response and progression at each treatment cycle. To further ascertain the similarity in response endpoints for MonumenTAL-1 and MajesTEC-1, the timing between visits was assessed.

Endpoints included in the comparative analyses were defined in the same way (see Table 6). For DOR, TTNT and OS, censoring was applied in the same way for both MonumenTAL-1 and MajesTEC-1. Response rates and PFS were adjudicated by the IRC for both MonumenTAL-1 and MajesTEC-1.

7.1.2 Method of synthesis

Individual patient-level data for talquetamab (MonumenTAL-1) with follow-up time to 17 January 2023 (Janssen 2023e) and teclistamab (MajesTEC-1) with follow-up to 4 January 2023 (Janssen 2023c) for patients with relapsed or refractory multiple myeloma were used in adjusted comparisons, wherein treatment cohorts were balanced on baseline prognostic factors. Baseline prognostic factors considered for statistical adjustment were selected a priori based on feedback from clinical experts. Adjusted comparisons were conducted using IPTW with ATC weights in the main analyses, meaning that the MonumenTAL-1 population was adjusted whereas MajesTEC-1 remained unaltered; ATT weights were applied in sensitivity analyses; ATT weights is the opposite to ATC weights, meaning that that the MajesTEC-1 population was adjusted whereas the MonumenTAL-1 remained unaltered.

The comparative effectiveness of talquetamab administered at 0.8 mg/kg Q2W SC versus teclistamab was assessed for the following endpoints: ORR, CR or better rate, VGPR or better rate, DOR, PFS, TTNT, and OS. The main analysis adjusted for refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines of therapy, age, haemoglobin, LDH, creatinine clearance, ECOG score, sex, type of multiple myeloma prior stem cell transplant, race and cytogenetic profile. A range of sensitivity analyses were conducted to assess the robustness of findings from the main analysis. E-values were calculated to assess the potential impact of unmeasured confounding on the overall study conclusions.

For a full description of the methodology used, see Appendix C.

7.1.3 Results from the comparative analysis

Results from the comparative analyses of Talquetamab vs teclistamab for triple-exposed RRMM patients are shown in Table 15.

For detailed descriptions of the results, see Appendix C.

Table 15. Results from the comparative analysis of talquetamab 0.8 mg/kg Q2W vs. teclistamab for triple exposed RRMM patients (main analysis: IPTW – ATT)

Outcome measure	Talquetamab adjusted (IPTW ATC) 0.8 mg/kg Q2W (N=145)	Teclistamab (N=165)	Relative effect	Absolute effect
ORR	[redacted]	104/165 (63.03%)	[redacted]	[redacted]
CR or better rate		75/165 (45.45%)		
VGPR or better rate		98/165 (59.39%)		
DOR		Median: 21.55 months (95% CI: 16.23, NE)		
PFS (IRC)		Median: 11.30 months (95% CI: 8.77, 16.36)		
TTNT		Median: 12.68 months (95% CI: 8.71, 17.61)		
OS		Median: 21.91 months (95% CI: 15.08, NE)		

Abbreviations: CR, Complete response; DOR, Duration of response; IRC, Independent Review Committee; ORR, Overall response rate; OS, overall survival; PFS, progression-free survival; VGPR, Very good partial response.

Time point of analysis: Data used in the analysis was based on MonumenTAL-1 data-cut of January 2023 (talquetamab 0.4 mg/kg Q1W median duration of follow-up: 18.8 months) and MajesTEC-1 data-cut of January 2023 (22.8 months).

Note: *Due to the weighting performed, n does not add up to an even number.

7.1.4 Efficacy – results per [outcome measure]

N/A. See section 7.1.3.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

The relative effectiveness used in the model was sourced from clinical studies, MonumenTAL-1 for talquetamab and MajesTEC-1 for teclistamab. Data cuts from January 2023 were used for both MonumenTAL-1 and MajesTEC-1. Efficacy and safety data from the MonumenTAL-1 trial was based on Cohort C (0.8 mg/kg Q2W) since this dosing and administration interval is expected to constitute the relevant dosing and administration interval in a Danish context. Additional sources include Danish life tables for background mortality (Statistics Denmark 2023).

Time to event data were extrapolated over the time horizon of the analysis. OS and PFS were modelled using parametric survival distributions fitted to available individual patient data (IPD), from the studies. Though, the MonumenTAL-1 data had been adjusted through IPTW with ATC weights. Standard parametric models were fitted to the adjusted 0.8 mg/kg Q2W MonumenTAL-1 cohort and the unadjusted MajesTEC-1 cohort. In addition to OS and PFS, the event of treatment discontinuation (time to treatment discontinuation, TTTD) was also extrapolated over the time horizon of the analysis.

Standard parametric survival models including exponential, Gompertz, Weibull, log-logistic, lognormal, gamma and generalised gamma were fitted to the data (PFS, OS and TTTD). The selection of survival models for the base case was based on multiple criteria, including goodness-of-fit statistics (Akaike Information Criteria [AIC], supported by the Bayesian Information Criteria [BIC]), visual fit comparing the projected survival and the empirical Kaplan-Meier curve and smoothed hazard curves from MonumenTAL-1 and MajesTEC-1. In addition, the clinical plausibility of the projections of events for the different models was considered. Lastly, in accordance with NICE guidelines it was preferred to apply the same distribution for the two treatment arms unless there was strong evidence for the contrary (Latimer 2011).

Survival curves were fitted individually to talquetamab and teclistamab.

The hazard of death at each cycle was adjusted by taking the maximum hazard per cycle of general population mortality and the hazard implied by the parametric extrapolation (i.e., the predicted risk of either progressing and/or dying could not fall below the mortality risk in the general population).

Teclistamab was recently evaluated by DMC for the same indication as this application is pertaining to, based on the pivotal MajesTEC-1 trial. The health economic analysis in this application was carried out in the MajesTEC-1 population; MajesTEC-1 population remained unaltered while the MonumenTAL-1 was adjusted to fit the MajesTEC-1 population. OS, PFS and TTTD in the teclistamab arm was extrapolated with the same parametric distributions as was used by DMC in their evaluation of teclistamab; the DMC established two scenarios in their evaluation of teclistamab, one more optimistic and one more conservative; within the more optimistic scenario, OS, PFS and TTTD was all extrapolated through application of the lognormal

distribution, while in the more conservative scenario OS was extrapolated by the Weibull distribution, PFS by the gamma distribution and TTTD by the exponential distribution. Teclistamab in the current application was based on DMC's more optimistic scenario, since establishing an analysis in which talquetamab is favourable to the conservative teclistamab outcomes does not by necessity yield superiority versus the more optimistic scenario and having talquetamab resulting in worse outcomes than teclistamab would be clinically implausible, considering the outcomes presented in section 7; additionally, comparing talquetamab to teclistamab modelled according to the more optimistic scenario from the teclistamab evaluation should be viewed as conservative as the ICER of teclistamab versus physician's choice was lower in the more optimistic than in the more conservative scenario. The notion of benchmarking the teclistamab OS, PFS and TTTD curves in the current application with the OS, PFS and TTTD curves from the teclistamab application, regardless of if the more optimistic or pessimistic scenario was used as the benchmark, was the implausibility of assuming different OS, PFS and TTTD curves when the already established curves have not been refuted by new clinical data; why would OS, PFS and TTTD of teclistamab treated patients within the MajesTEC-1 population differ when it is compared to talquetamab instead of physician's choice if all else is equal?

The survival analysis from Janssen's teclistamab application as well as the DMC's evaluation of that analysis is found in Appendix D.

8.1.1.1 Extrapolation of Overall Survival (OS)

Error! Reference source not found. summarises the assumptions associated with extrapolation of overall survival. Supplementary tables and figures with AIC and BIC statistics, comparison of visual fits on observed OS rates and hazard functions are presented in Appendix D. The long-term OS extrapolations for talquetamab and teclistamab are presented in Figure 9.

OS in the teclistamab arm was extrapolated by applying the lognormal distribution, in line with the DMC's evaluation of teclistamab.

According to AIC and BIC, the lognormal and the exponential distribution respectively had the best fit for talquetamab. However, all distributions had ΔAIC<2, implying there being substantial (goodness-of-fit) statistical support for all of them (Burnham and Anderson 2004). Visually, all distributions provided a good fit to the Kaplan-Meier survival curve, in part a result of the curves starting to diverge in the time-periods following the last time-period for which there is a Kaplan-Meier estimate. Though the exponential distribution had a slightly worse visual fit than the other distributions.

The lognormal survival curve is one of the more optimistic curves while the exponential is the most conservative, in the sense of OS survival rates. The smoothed hazards from MonumenTAL-1 are decreasing over time, which fits well to the hazard function of the lognormal distribution but poorly to the hazard function of the exponential distribution, since the latter yields a constant hazard over time. All distributions except the exponential distribution had hazard functions relatively aligned with the smoothed hazard from MonumenTAL-1, decreasing as time ensues.

The lognormal, loglogistic, Gompertz and generalised gamma distributions were all deemed clinically implausible despite their hazards fitting relatively well to the smoothed hazard from MonumenTAL-1, because the survival curves generated by these distributions resulted in more optimistic curves than what the DMC applied for ciltacabtagene autoleucel in their evaluation of the same pharmaceutical for the same indication as talquetamab is currently being evaluated for; there is to date no clinical data supporting preferable outcomes in favour of talquetamab versus ciltacabtagene autoleucel.

The rejection of the lognormal, loglogistic, Gompertz and generalised gamma distributions limits the assortment to the Weibull, exponential and gamma distribution, which are generating the three least optimistic survival curves. The exponential distribution was rejected, in part because as previously mentioned its hazard function did not fit to the smoothed hazard from MonumenTAL-1. Additionally, selecting it would result in a survival curve which is crossing the OS curve of the teclistamab arm (based on the lognormal distribution) after approximately eight years from treatment initiation; having an OS curve of one treatment arm crossing the OS curve of another treatment arm is not per definition clinically implausible but for talquetamab versus teclistamab it is clinically implausible since a clear and statistically significant survival benefit have been shown for the former versus the latter. The survival curves generated by the Weibull and gamma distributions also intersecting the OS curve of the teclistamab arm but at substantially later time-points, after approximately 17 and 13 years respectively.

For the base case analysis, the Weibull distribution was selected to extrapolate OS in the talquetamab arm, ahead of the gamma distribution. The former was selected ahead of the latter because of two reasons: (1) Slightly lower AIC- and BIC-values and (2) The intersection of the teclistamab OS curve by the talquetamab occurs at a later time-point.

Because there is no data supporting converging and crossing of the OS curves, a functionality was applied in the base case analysis which ensured the talquetamab OS curve to never fall below the teclistamab OS curve. This functionality can be turned off. The gamma distribution was utilized in a scenario analysis.

The lognormal distribution was also applied in a scenario analysis, because it has the best goodness-of-fit according to AIC, its hazard function provided good fit to the smoothed hazard from MonumenTAL-1, and its utilization results in homogeneity distribution-wise between the two treatment arms which is in line with the NICE guidelines (Latimer 2011).

Table 16. Summary of assumptions associated with extrapolation of Overall Survival

Method/approach	Description/assumption
Data input	Talquetamab: MonumenTAL-1 Teclistamab: MajesTEC-1
Model	Fully parametric distributions were fitted individually for talquetamab and physician's choice, respectively.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Talquetamab: Lognormal Teclistamab: Lognormal
Function with best BIC fit	Talquetamab: Exponential Teclistamab: Lognormal
Function with best visual fit	Intervention: Not exponential Teclistamab: Not exponential
Function with the best fit according to external evidence	Lognormal, loglogistic, Gompertz and generalised gamma were not considered for the talquetamab arm based on comparison to ciltacabtagene autoleucel-treated patients
Function with best fit according to evaluation of smoothed hazard assumptions	Talquetamab: Lognormal/Gompertz/Generalised Gamma Teclistamab: Undetermined
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No

Method/approach	Description/assumption
Assumptions of cure point	No
Selected parametric function in base case analysis	Talquetamab: Weibull Teclistamab: Lognormal
Validation of selected extrapolated curves	Weibull is one of the more conservative curves for talquetamab, while also having ΔAIC of <2, a hazard function fitting with the smoothed hazard from MonumenTAL-1 (decreasing over time), and only a relatively minor issue of its OS curve crossing the OS curve of the teclistamab arm. Lognormal is the same distribution which was used by the DMC to extrapolate OS of teclistamab in their recent evaluation of it in the same patient population.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival; TLV: Tandvårds- och läkemedelsförmånsverket

Figure 9. Long-term OS projection of Talquetamab 0.8 mg/kg Q2W (MonumenTAL-1, IPTW-ATC adjusted) and Teclistamab (MajesTEC-1)

8.1.1.2 Extrapolation of Progression-Free Survival (PFS)

Table 17 summarises the assumptions associated with extrapolation of PFS. Supplementary tables of AIC/BIC statistics, comparison of visual fits on observed PFS rates and hazard functions are presented in Appendix D. The long-term PFS extrapolations for talquetamab and teclistamab are presented in Figure 10.

PFS in the teclistamab arm was extrapolated by applying the lognormal distribution, in line with the DMC's evaluation of teclistamab.

Despite the lack of statistical significance in the PFS endpoint for talquetamab versus teclistamab, the numerical advantage was substantial. In addition, there was a statistically significant advantage for talquetamab in the OS endpoint. Combined, this indicated a clear trend in favour for talquetamab and thus an efficacy difference in PFS was included in the cost-effectiveness

analysis. However, a scenario analysis was carried out in which PFS of talquetamab was assumed to equal PFS of teclistamab. In this scenario analysis the TTTD curve was adjusted as well, to reduce bias.

According to AIC, the generalised gamma distribution had the best fit for talquetamab, followed by the lognormal distribution; these two distributions where the only two distributions which had ΔAIC of <2, implying that all other distributions had substantially less statistical support (Burnham and Anderson 2004). Considering BIC, the lognormal distribution had the best fit for talquetamab, followed by the generalised gamma distribution. Visually, all distributions provided a good fit to the Kaplan-Meier survival curve; though Gompertz and generalised gamma better than the other. Visually comparing the smoothed hazard from MonumenTAL-1 to the hazard functions of the distributions provided a slightly different picture than the AIC and BIC comparison, all distributions except the exponential did provide hazard functions with relatively good fit to the smoothed hazard from MonumenTAL-1; the overarching trend of the hazards of these distributions was decreasing as time ensues and so was trend of the smoothed hazard, while the exponential distribution was associated with an invariable hazard.

The Gompertz distribution yielded a clinically implausible plateau for talquetamab. The generalised gamma distribution yielded a survival curve more optimistic compared to what the DMC determined for ciltacabtagene autoleucel in their evaluation of the same pharmaceutical and as for OS there is no data supporting superior outcomes for talquetamab over ciltacabtagene autoleucel, rendering the generalised gamma distribution clinically implausible; the Gompertz distribution also resulted in a PFS curve superior to the DMC's PFS curve for ciltacabtagene autoleucel. The Weibull, exponential and gamma distributions all generate PFS curves inferior to the PFS curve of the teclistamab arm, rendering these distributions clinically implausible.

The lognormal and loglogistic distributions yields PFS curves only slightly superior to the PFS curve of the teclistamab arm. Considering the numerical, but statistically insignificant, superiority of talquetamab versus teclistamab, with respect to PFS, applying only a minor PFS benefit was deemed clinically plausible. The lognormal distribution was selected for the extrapolation of PFS in the talquetamab in the base case analysis, ahead of the loglogistic distribution because: (1) better statistical fit and (2) Consistency, distribution-wise, with the control-arm, which is preferred according to NICE (Latimer 2011).

Table 17. Summary of assumptions associated with extrapolation of Progression-Free Survival

Method/approach	Description/assumption
Data input	Talquetamab: MonumenTAL-1 Teclistamab: MajesTEC-1
Model	Fully parametric distributions were fitted individually for talquetamab and teclistamab, respectively
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Talquetamab: Generalised gamma Teclistamab: Generalised gamma
Function with best BIC fit	Talquetamab: Lognormal Teclistamab: Lognormal
Function with best visual fit	Talquetamab: Gompertz and generalised gamma Teclistamab: Not exponential
Function with the best fit according to external evidence	Not Gompertz nor generalised gamma, based on comparison to ciltacabtagene autoleucel-treated patients
Function with best fit according to evaluation of smoothed hazard assumptions	Talquetamab: Not exponential Teclistamab: Not exponential
Adjustment of background mortality with data from Statistics Denmark	Yes

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Talquetamab: Lognormal Physician's choice: Lognormal
Validation of selected extrapolated curves	-

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 10. Long-term PFS IRC projection of Talquetamab 0.8 mg/kg Q2W (MonumenTAL-1, IPTW-ATC adjusted) and Teclistamab (MajesTEC-1)

8.1.1.3 Extrapolation of Time To Treatment Discontinuation (TTTD)

The base case uses TTTD curves for the treatment duration of both talquetamab (MonumenTAL-1) and the comparator (MajesTEC-1) to determine the time on treatment more accurately. Supplementary tables of AIC/BIC statistics, comparison of visual fits on observed TTTD rates and hazard functions are presented in Appendix D. The long-term TTTD extrapolations for talquetamab and teclistamab are presented in Figure 11.

The model includes the possibility to extrapolate TTTD using the standard parametric models. TTTD curves were capped to PFS within the model and assumed to follow the same distribution as PFS (Lognormal) because these two outcomes are heavily interlinked. In the talquetamab arm, lognormal was the distribution with the best goodness-of-fit according to AIC, followed by loglogistic and generalised gamma; lognormal and loglogistic were the only distributions with ΔAIC<2, while generalised gamma had ΔAIC=2. According to BIC, the exponential distribution had the best statistical fit, followed by the lognormal distribution.

A result of the selected parametric distributions is intersection of the TTTD curves, which was not entirely unexpected considering that the Kaplan-Meier curves are intersecting each other and

there being a higher degree of treatment discontinuation due adverse events in MonumenTAL-1 compared to MajesTEC-1; 8.3% of the patients in the bi-weekly cohort (cohort C [0.8 mg/kg Q2W SC cohort]) from MonumenTAL-1 discontinued treatment due though adverse events, while 4.8% of the patients in MajesTEC-1 discontinued treatment due to adverse events. (Janssen 2023e) and (Janssen 2023c).

Figure 11. Long-term TTTD projection of talquetamab 0.8 mg/kg Q2W (MonumenTAL-1 Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC, ATC weighted) and teclistamab (MajesTEC-1)

8.1.2 Calculation of transition probabilities

Not applicable, transition probabilities were not calculated within the PSM model.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Subsequent treatment impacts costs but not survival outcomes in the model.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Modelled OS, PFS and TTTD without half cycle-correction and discounting but with adjustment for background mortality of the Danish population are presented in Table 18, Table 19 and Table 21 respectively.

Table 18. OS estimates in the model, undiscounted and without half-cycle correction

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median from relevant study
Talquetamab 0.8mg/kg Q2W (ATC weighted)	[redacted]		
Teclistamab			

Abbreviations: OS: Overall survival

Table 19. PFS estimates in the model, undiscounted and without half-cycle correction

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from relevant study
Talquetamab 0.8mg/kg Q2W (ATC weighted)	[redacted]		
Teclistamab			

Abbreviations: PFS: Progression-free survival

Table 20. TTTD estimates in the model, undiscounted and without half-cycle correction

	Modelled average TTTD (reference in Excel)	Modelled median TTTD (reference in Excel)	Observed median from relevant study
Talquetamab 0.8mg/kg Q2W (ATC Weighted)	[redacted]		
Teclistamab			

Abbreviations: TTTD: Time to treatment discontinuation

Treatment length was modelled using time to treatment discontinuation. Table 21 shows the mean time in treatment, in PFS and in post-progression state.

Table 21. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length	PFS	PPS
Talquetamab 0.8mg/kg Q2W (ATC weighted)	[redacted]		
Teclistamab			

9. Safety

9.1 Safety data from the clinical documentation

Table 22. Overview of safety events. From study start to January 2023 data cut.

	Safety Events				Risk Difference vs Teclistamab	
	Talquetamab 0.8 mg/kg		Teclistamab		Talquetamab 0.4 mg/kg	Talquetamab 0.8 mg/kg
	N=145		N=165			
	n	*%*	*n*	*%*	% [95% CI]	% [95% CI]
Number of adverse events	3733		4855		[redacted]	
Number and proportion of patients with ≥1 adverse events	145	100.0%	165	100.0%		
Number of serious adverse events	124		362			
Number and proportion of patients with ≥ 1 serious adverse events*	70	48.3%	113	68.5%		
Number of CTCAE grade ≥ 3 events	622		1372			
Number and proportion of patients with ≥ 1 CTCAE grade >=3 events	113	77.9%	156	94.5%		
Number of CTCAE grade 3/4 events	616		1338			
Number and proportion of patients with ≥ 1 CTCAE grade 3/4 events	113	77.9%	156	94.5%		
Number of adverse reactions, n						

Number and proportion of patients with ≥ 1 adverse reactions					[redacted]
Number and proportion of patients who had a dose reduction	13	9.0%	1	0.6%	
Number and proportion of patients who discontinue treatment regardless of reason	85	58.6%	90	54.5%	
Number and proportion of patients who discontinue treatment due to adverse events	12	8.3%	8	4.8%	

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

Table 23. Serious adverse events (≥5% Any Grade (time point)

Adverse events	Talquetamab 0.8 mg/kg Q2W (N=145)		Teclistamab	(N=165)
	Number of patients with adverse events		Number of patients with adverse events	
Total number of participants with 1 or more serious TEAE	70	48.3%	113	68.5%
MedDRA system organ class/preferred term				
Infections and infestations	23	15.9%	78	47.3%
Immune system disorders	15	10.3%	14	8.5%
Cytokine release syndrome	15	10.3%	14	8.5%
General disorders and administration site conditions	8	5.5%	23	13.9%

Pyrexia	7	4.8%	10	6.1%
Nervous system disorders	13	9.0%	13	7.9%
Respiratory, thoracic and mediastinal disorders	6	4.1%	14	8.5%

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

The model considers the costs and HRQoL impact of safety of the first treatment. AEs due to subsequent treatments were not considered in the model, as the model assumes the same distribution of subsequent treatments across comparators in the base case. Additionally, costs and utility decrements for AEs are not expected to be substantial model drivers.

Treatment-emergent adverse events were included as they affect both costs and quality of life of patients receiving treatment. AEs were only considered for the initial treatment. Except for CRS, AEs rates were limited to those of grade 3 or higher. For CRS, Grade 1-2 events were included as well as Grade 3+, and no minimum incidence criterion was used.

Table 24. Adverse events used in the health economic model

Adverse events	Talquetamab	Teclistamab		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Anemia	27.6%	37.6%	MonumenTal-1, MajesTEC-1	Only treatment-emergent adverse events were included
CRS, Grade 1-2	73.8%	71.5%		
CRS, Grade 3+	0.7%	0.6%		
Hypertension	3.4%	6.1%		
Hypokalemia	5.5%	4.8%		
Hypophosphatemia	7.6%	6.7%		
Leukopenia	12.4%	9.1%		
Lymphopenia	26.9%	34.5%		
Neurotoxicity, Grade 1-2	29.7%	15.8%		
Neurotoxicity, Grade 3+	4.8%	0.6%		
Neutropenia	22.1%	65.5%		
Pneumonia	2.1%	13.3%		
Thrombocytopenia	18.6%	22.4%		

9.2 Safety data from external literature applied in the health economic model

No external safety data is used in the health economic model.

10. Documentation of health-related quality of life (HRQoL)

All health-related quality of life (HRQoL) data were based on EQ-5D-5L from the trial MonumenTAL-1.

Table 25. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	MonumenTAL-1, MajesTEC-1	Instrument used to elicit health state utility values

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

In the MonumenTAL-1 clinical trial and the MajesTEC-1 clinical trial, patients completed patient-reported outcome measures related to their HRQoL, including the EORTC-QLQ-C30, Patient Global Impression of Severity (PGIS), and the EuroQoL Five-Dimension (EQ-5D-5L). In the main indirect comparison, which is the foundation of the health economic analysis, the MonumenTAL-1 population was adjusted to fit the MajesTEC-1 population, therefore the utilities for the PF and PD health state were obtained from MajesTEC-1 EQ-5D-5L data (January 2023 data cut). A justification for applying the same utilities for both treatment arms are provided in section 0.

10.1.2 Data collection

In MonumenTAL-1, EQ-5D-5L data were collected at the following time points:

- Baseline (after the subject signed informed consent and before any procedures scheduled for the same day as the PRO assessments were collected),
- Day 1 of every uneven cycle during treatment (i.e., Day 1 of Cycles 1, 3, 5, 7, 9, 11 etc.),
- Every 16 weeks (±2 weeks) post initial indication of progressive disease or end of treatment (whichever occurred first).

In MajesTEC-1, EQ-5D-5L data were collected at the following time points:

- Baseline (after the subject signed informed consent and before any procedures scheduled for the same day as the PRO assessments were collected),
- Day 1 of every even 28-days cycle during treatment (i.e., Day 1 of Cycles 2, 4, 6, 8, 10 etc.),
- Every 16 weeks (±2 weeks) post initial indication of progressive disease or end of treatment (whichever occurred first).

These instruments were completed by patients before any clinical tests, procedures or other consultations that would influence the patients' perceptions of their current health state.

Error! Reference source not found. shows the pattern of missing EQ-5D data from MonumenTAL-1 for cohort C (talquetamab 0.8mg/kg Q2W). **Error! Reference source not found.** shows the pattern of missing EQ-5D data from MajesTEC-1 (teclistamab).

Table 26. Pattern of missing data and completion, MonumenTAL-1 talquetamab, Cohort C

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	109	4 (3.7%)	109	105 (96.3%)
Treatment cycle 1	109	15 (13.8%)	103	88 (85.4%)
Treatment cycle 3	109	17 (15.6%)	85	68 (80.0%)
Treatment cycle 5	109	13 (11.9%)	76	63 (82.9%)
Treatment cycle 7	109	16 (14.7%)	72	56 (77.8%)
Treatment cycle 9	109	15 (13.8%)	67	52 (77.6%)
Treatment cycle 11	109	24 (22.0%)	53	29 (54.7%)
Treatment cycle 13	109	14 (12.8%)	34	20 (58.8%)
Treatment cycle 15	109	10 (9.2%)	15	5 (33.3%)

Table 27. Pattern of missing data and completion, MajesTEC-1 teclistamab

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	125	29 (23.2%)	125	96 (76.8%)
Treatment cycle 2	125	15 (12.0%)	94	79 (84.0%)
Treatment cycle 4	125	12 (9.6%)	81	69 (85.2%)
Treatment cycle 6	125	19 (15.2%)	77	58 (75.3%)
Treatment cycle 8	125	15 (12.0%)	73	58 (79.5%)
Treatment cycle 10	125	21 (16.8%)	66	45 (68.2%)
Treatment cycle 12	125	20 (16.0%)	59	39 (66.1%)
Treatment cycle 14	125	23 (18.4%)	55	32 (58.2%)
Treatment cycle 16	125	16 (12.8%)	52	36 (69.2%)
Treatment cycle 18	125	17 (13.6%)	46	29 (63.0%)
Treatment cycle 20	125	13 (10.4%)	39	26 (66.7%)
Treatment cycle 22	125	20 (16.0%)	38	18 (47.4%)
Treatment cycle 24	125	26 (20.8%)	31	5 (16.1%)

10.1.3 HRQoL results

For the PF health state, time-dependent and non-time-dependent utilities were estimated based on MonumenTAL-1 Cohort C (talquetamab 0.8mg/kg Q2W) and MajesTEC-1. For the PD health state non-time-dependent utilities were estimated based on the same data sources. Comparing the mean values there was a numerical but non-significant (95% CI) difference between talquetamab and teclistamab, in favour of the latter (see Table 28 for a comparison of Cohort C from MonumenTAL-1 and MajesTEC-1); a formal comparison of the time-dependent utilities were not possible because data

collection occurred at different time-points, every uneven week in MonumenTAL-1 and every even week in MajesTEC-1. However a naïve comparison of the time-dependent mixed model for repeated measures (MMRM) based utilities are presented in Figure 12.

Figure 12. Naïve comparison of time-dependent MMRM based utilities

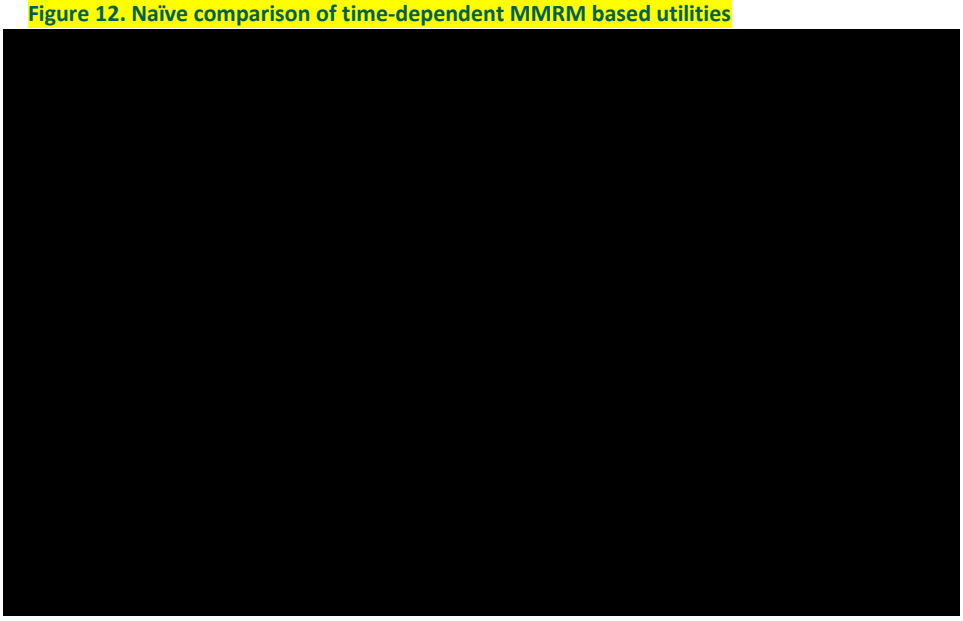


Table 28. EQ-5D-5L comparison of pre-progression patients, MonumenTAL-1 versus MajesTEC-1

	Talquetamab				Teclistamab				Difference in least square mean CFB
			MMRM estimates (overall period)				MMRM estimates (overall period)		
Outcome measue	n	Mean at baseline	Least squares mean (SE) [95%CI], p-value	Least squares mean CFB (SE) [95%CI], p-value	n	Mean at baseline	Least squares mean (SE) [95%CI], p-value	Least squares mean CFB (SE) [95%CI], p-value	Estimate [95%CI], p-value
EQ-5D-5L utility (Danish tariff), unadjusted	94	[redacted]							
EQ-5D-5L utility (Danish tariff), adjusted	94								

Considering the lack of a significant difference between the utilities, there was no need for treatment specific utilities. For the PF health-state, time-dependent utilities were estimated and applied in the health economic analysis; the utilities were based on MajesTEC-1 instead of MonumenTAL-1 because the analysis is carried out within the MajesTEC-1 population. For the PD health-state, a single non-time-dependent utility, based on data from patients who progressed in MajesTEC-1, was utilized. A mixed-model-repeated-measures (MMRM) model was used to estimate both the PF and PD utility estimates. MonumenTAL-1 utilities are presented in Appendix F.

Error! Reference source not found. presents the applied time-dependent PF health state utility values derived by the Danish preference weight, based on EQ-5D-5L questionnaires from patients in MajesTec-1; the health economic model linearly interpolates utility values to obtain model cycle specific utilities; the second to latest time-dependent utility estimate (0.890) was then carried forward. As shown, average PF utility increased with time since treatment start.

Table 29. Time-dependent utilities in pre-progression state (based on mixed model for repeated measures [MMRM])

Time (days)	Time (28 days)	n	Mean	SE	Lower 95% CI	Upper 95% CI
0	0	96	[redacted]			
56	2	80				
112	4	66				
168	6	64				
224	8	61				
280	10	56				
336	12	50				
392	14	46				
448	16	44				
504	18	41				
560	20	35				
616	22	34				
672	24	28				

* The latest cycle estimate is based on a s[redacted]
utility and the utilities of the following cycles was assumed to be equal to the previous cycle estimate (0.8753).

The utility of the PF health-state is presented in Table 30.

Table 30. MajesTEC-1 post-progression index score

Health state	n	Mean	SE	Lower 95% CI	Upper 95% CI
Post progression survival	23	0.740	0.061	0.621	0.859

The mapping algorithm to Danish utilities is described in section 0.

10.1.4 HSUV calculation

As previously mentioned, treatment-specific utility weights were not used within the analysis, thus patients from the two treatment arms were assumed to have the same degree of health-related quality of life when they belonged to the same health state.

To capture the impact of increasing utility estimates in the PF state, the model base case applied time-dependent utilities. However, a single PD utility value was assigned to all patients in the post-progression health state.

AE-related utility decrements were calculated for a specified duration and applied as a one-off upon the start of the PF state (see section 0 for more information).

A drawback of using PF utilities estimated using a single MMRM in the model, is that observations from patients who progressed early would still impact pre-progression utility estimates in later time points, because MMRM assumes that observations over time from the same patient are correlated (within subject correlation).

Treatment cycle specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a treatment cycle do not influence the utility estimate for that cycle: First, for each EQ-5D-5L collection time point, a separate MMRM was fitted using information only from patients who stayed progression free until that time point, including all their available EQ-5D-5L results (including baseline) up to and including that time point, using visit as a categorical predictor, to get time specific utility estimates. Second, from each of these MMRMs, the least squares (LS) mean estimate of the last time point was used as the utility estimate for that time point in the cost effectiveness model. These time specific LS estimates (each of which was obtained from a different MMRM) are provided in Table 32. Each of the MMRMs had the autoregressive variance covariance structure, which assumes that variances are homogenous and correlations between measurements over time decline exponentially. This means that variability of utility measurements is constant at each treatment cycle, and measurements next to each other are more correlated with each other compared with measurements further apart from each other.

Age adjustment for health state utility values (HSUV) was implemented in the base case analysis according to the DMC guidelines. When calculating the HSUV over time, the multiplicative method was used. The DMC has provided Danish standard values (Table

31) which were used to calculate an index which was be applied to the QALYs over time (Medicinrådet 2023a). The age-adjustment was done using the Danish general population utilities stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age.

Table 31. Danish general population utility values stratified by age groups

Age group	Utility values
0-17	[redacted]
18-29	
30-39	
40-49	
50-69	
70-79	
80+	

10.1.4.1 Mapping

EQ-5D-5L utility scores were derived using preference weights based on the general Danish population. Mapping was performed based on DMC methods guide for assessing new pharmaceuticals (Medicinrådet 2021), stating that preference weights based on the general Danish population (Jensen et al. 2023) should be used to calculate health-related quality of life. The method used to map utilities is described in Appendix K.

10.1.5 Disutility calculation

Utility decrements due to AEs were sourced from publications and previous HTA submissions (see Table 32). The duration of utility decrements was based on MonumenTAL-1. Utility decrements were applied as one-time decrements in baseline utility value at the start of the PSM. For Grade 3+ CRS events, a utility decrement equal to that of the PFS health state utility is assumed, resulting in a utility of 0.00 (zero) for patients for the duration of these events. This assumption is consistent with previous models (Hettle et al. 2017, National Institute for Health and Care Excellence (NICE) 2019a).

10.1.6 HSUV results

Table 32 presents the HSUVs used in the model. Only data for Cohort C (0.8 mg/kg Q2W) were used in the model (numbers are also presented in **Error! Reference source not found.**).

Table 32. Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PFS (per cycle)				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
0	0.706 (0.6455, 0.7669)			
2	0.757 [0.6938, 0.8210]			
4	0.827 [0.7627, 0.8903]			
6	0.811 [0.7451, 0.8769]			
8	0.855 [0.7900, 0.9202]			
10	0.841 [0.7690, 0.9134]			
12	0.833 [0.7549, 0.9113]	EQ-5D-5L	DK	Estimates are based on MajesTEC-1.
14	0.871 [0.7859, 0.9557]			
16	0.832 [0.7508, 0.9126]			
18	0.846 [0.7608, 0.9316]			
20	0.893 [0.8156, 0.9699]			
22	0.875 [0.7936, 0.9570]			
24	0.875 [0.7936, 0.9570]			
PPS	0.740 [0.621, 0.859]	EQ-5D-5L	DK	Estimates are based on MajesTEC-1.
Adverse event disutilities				
aPTT increased	-0.0700 [SE uknown]	EQ-5D-3L	UK	Assumed lowest in range, Brown 2013 (Bacelar et al. 2014)
Anemia	-0.3100 [SE uknown]			(Ossa et al. 2007)
AST increased	-0.0700 [SE uknown]			Assumed lowest in range, Brown 2013 (Bacelar et al. 2014)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Asthenia and fatigue	-0.1200 [SE uknown]			(Lloyd et al. 2006)
CRS, Grade 1-2	-0.1109 [SE uknown]			CARTITUDE-1
CRS, Grade 3+	-0.637 [SE uknown]			Assumed to be equal in magnitude to the utility value in the progression-free health state, per (Hettle et al. 2017)
Diarrhea	-0.1000 [SE uknown]			(Lloyd et al. 2006)
Dyspnea	0			Assumption
Febrile neutropenia	-0.3900 [SE uknown]			Launois et al., 1996 (Launois et al. 1996)
Gamma-glutamyltransferase increased	-0.0700 [SE uknown]			Assumed lowest in range, Brown 2013 (Bacelar et al. 2014)
Hyperglycemia	-0.0710 [SE uknown]			(Smith-Palmer et al. 2016)
Hypertension	0 [SE uknown]			Assume no QoL impact, controlled by medication, in accordance with NICE appraisal TA573 (Table 46 Committee papers) (National Institute for Health and Care Excellence (NICE) 2023)
Hypokalemia	-0.2000 [SE uknown]			Clinical opinion, used in NICE appraisal TA510 of daratumumab 2019 (Table 60 Appraisal consultation committee papers) (National Institute for Health and Care Excellence (NICE) 2018)
Hyponatremia	0			Assumption
Hypophosphatemia	-0.1500 [SE uknown]			Assumption
Infections - Pathogen unspecified	-0.1900 [SE uknown]			Assumed the same as pneumonia
Keratopathy	0			Assumption
Leukopenia	-0.0700 [SE uknown]			No data found. Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. 2014)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Lymphopenia	-0.0700 [SE uknown]			No data found. Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. 2014)
Mental status changes	0			Assumption
Nausea	0			Assumption
Neurotoxicity, Grade 1-2	0			Assumed to be captured as part of CRS disutility
Neurotoxicity, Grade 3+	0			Assumed to be captured as part of CRS disutility
Neutropenia	-0.1500 [SE uknown]			Brown 2013/Partial Review TA171 (Bacelar et al. 2014)
Pneumonia	-0.1900 [SE uknown]			Brown 2013/Partial Review TA171 (Bacelar et al. 2014)
Pyrexia	-0.0700 [SE uknown]			No data found. Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. 2014)
Sepsis	-0.2000 [SE uknown]			Tolley et al. 2013 (Tolley et al. 2013)
Thrombocytopenia	-0.3100 [SE uknown]			Assume same disutility as anemia (Ossa et al. 2007).
Viral infection	-0.1900 [SE uknown]			Assumed the same as pneumonia

Abbreviations: AST: Aspartate aminotransferase; CI: Confidence Interval; CRS: Cytokine release syndrome; DK: Denmark; PFS: Progression-Free Survival; PPS: Post-Progression Survival

Note: The latest cycle estimate is based on a small number of patients, in the health economic model the cycle 24 PF utility and the utilities of the following cycles was assumed to be equal to the previous cycle estimate (0.8753).

10.2 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

11. Resource use and associated costs

11.1 Pharmaceutical costs (intervention and comparator)

Patients on talquetamab were assumed to have 4 priming administrations (0.01, 0.06, 0.4, and 0.8 mg/kg), followed by a regimen of biweekly administrations (starting from week 3) (0.8 mg/kg) until progression.

Patients on teclistamab were assumed to have two priming administrations (6 and 30 mg/kg), followed by a regimen of weekly administrations (150 mg/kg) until disease progression. However, some patients were assumed to switch from weekly to bi-weekly administration (150 mg/kg), the number of patients switching and at which time-point was based on extrapolated data from MajesTEC-1 (see appendix D for further information).

Drug acquisition costs for talquetamab and teclistamab were based on the pharmacy purchase price (AIP). The base case assumes that 50% of patients vial share, regardless of if they are treated with teclistamab or talquetamab. The same vial sharing assumption was accepted by the DMC in the evaluation of teclistamab and has also been validated by Danish clinical expert. Wastage is calculated for the remaining 50% of patients. Dosing consumption per administration was rounded up to the closest integer number of vials. In the base case, dose intensity is assumed to be 100%, while it is assumed that 3.8% and 6.3% of drug administrations are skipped (for all administration routes) for talquetamab and teclistamab respectively, based on data from the MonumenTAL-1 and MajesTEC-1 clinical trials. Wastage and skipped administrations are accounted for to ensure accurate calculations of the true (real-world) treatment cost for an average patient. Table 33

Table 33 presents the treatment durations assumed for talquetamab and physician's choice. Treatment durations for talquetamab and teclistamab are modelled based on parametric curves fitted to TTTD of the MonumenTAL-1 trial and MajesTEC-1 trial respectively. TTTD curves were capped with PFS within the model and assumed the same distribution as PFS, to ensure avoidance of the TTTD curves intersecting the PFS curves (as described in section 8.1.1.3).

Table 33. Treatment Duration for talquetamab and teclistamab

Treatment regimen drug	Treatment duration
Talquetamab	Parametric curves fitted to TTTD
Teclistamab	Parametric curves fitted to TTD

Abbreviations: TTTD = time to treatment discontinuation

Table 34. Pharmaceutical costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]
Talquetamab (SC)	3.0 mg	1	2 834.05
	40.0 mg	1	37 747.30
Teclistamab (SC)	30 mg	1	6 733.03
	153 mg	1	34 338.46

11.2 Pharmaceutical costs – co-administration

Not applicable.

11.3 Administration costs

Table 35 shows the inputs used in the model for drug administration.

Talquetamab was assumed to be administrated subcutaneously for the entire dosing schedule. Talquetamab administration was assumed to require 7 days of hospital stay in week 1 and 1 day of hospital stay in week 2.

Teclistamab was assumed to be administrated subcutaneously for the entire dosing schedule. For the two priming dosing days and the first treatment dose, hospitalization is needed for at least 48 hours from start of injection. Therefore, the model assumed 4 days of hospital stay in the first cycle and 2 days of hospital stay in the second cycle.

The DRG 17MA98 was used to source the cost of administration (Sundhedsdatastyrelsen 2023). More specifically, based on DRG 17MA98 DRG 2023 "MDC17 1-dagsgruppe, pat. mindst 7 år", a cost of 2005 DKK was assumed for IV administration.

Due to lack of costs available for subcutaneous (SC) administration specifically, it was assumed that an SC administration was associated with 50% of the cost of IV administration (0.5*2005DKK=1002.5 DKK), given that IV is generally a more invasive administration form than SC.

For oral drug administration, no additional cost was assumed.

Table 35. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV administration	Each IV administration	2 005	17MA98	17MA98 DRG 2023 MDC17 1-dagsgruppe, pat. mindst 7 år
SC administration	Each SC administration	1 002.5	17MA98	50% of 17MA98 DRG 2023 MDC17 1-dagsgruppe, pat. mindst 7 år

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral drug administration	N/A	0	N/A	Assumption

Abbreviations: IV: intravenous; SC: Subcutaneous

11.4 Disease management costs

The model captures routine monitoring costs in the PFS and PPS state.

Table 36 presents the procedures and frequencies of medical resources. The types and frequencies of resources were based Internal Janssen Medical Advisor validation that confirmed that visits and test are done once per month (Janssen 2021). Post-progression frequency of resource use was assumed the same (once per month) as in pre-progression.

Disease management is assumed to be included when the patient visits healthcare for IV drug administration visits. Therefore, disease management costs are only included when patient had discontinued the initial treatment, and when patients are only treated with oral or SC drugs.

Table 36. Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Haematologist visit	every 4th week	1 066	N/A*	Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021
Full blood count	every 4th week	21.63	N/A	Ydelsesnummer 7110 - Takstkort 29A - Oktober 2022**
Biochemistry	every 4th week	21.63	N/A	Ydelsesnummer 7110 - Takstkort 29A - Oktober 2022**
24-hour urine protein electrophoresis sample	every 4th week	21.63	N/A	Ydelsesnummer 7110 - Takstkort 29A - Oktober 2022**
Urinary light chain excretion	every 4th week	28.84	N/A	Ydelsesnummer 7110 - Takstkort 29A - Oktober 2022**

*Not sourced from DRG codes **https://www.laeger.dk/media/sn5et2xh/takstkort-29-a-generelle-ydelser.pdf

11.5 Costs associated with management of adverse events

Costs of adverse events were sourced from the 2023 DRG codes. Table 40 shows the costs for the AEs. The incidence rate in Table 24 for adverse events was applied and its subsequent costs were modelled as a one-time cost per adverse event.

Table 37. Cost associated with management of adverse events

Adverse event	DRG code	Unit cost/DRG tariff
Anemia	16MA05	40 106 DKK

Adverse event	DRG code	Unit cost/DRG tariff
CRS, Grade 1-2	Assumption Fever, DRG 18MA04 divided by Trimpunkt 6	3 271 DKK
CRS, Grade 3+	18MA04	19 631 DKK
Hypertension	05MA11	17 304 DKK
Hypokalemia	23MA05	6 442 DKK
Hypophosphatemia	23MA05	6 442 DKK
Leukopenia	17MA05	18 627 DKK
Lymphopenia	17MA05	18 627 DKK
Neurotoxicity, Grade 1-2	21MA05	12 043 DKK
Neurotoxicity, Grade 3+	21MA06	19 041 DKK
Neutropenia	49PR07	19 588 DKK
Pneumonia	04MA13	41 804 DKK
Thrombocytopenia	16MA03	38 209 DKK

Abbreviations: AST: The aspartate aminotransferase; CRS: Cytokine release syndrome

11.6 Subsequent treatment costs

Subsequent treatment impacts costs but not survival outcomes in the model. The cost of subsequent treatments was applied as a one-off cost upon disease progression to a specified proportion of patients. Based on data from MonumenTAL-1 and MajesTEC-1, it was assumed in the base case that 77% in the talquetamab arm and 66% in the teclistamab arm of the progressing patients received a subsequent treatment line (Janssen 2023e, Janssen 2023c). The proportion of patients receiving a subsequent line of treatment was calculated by dividing the number of patients who had a record of a treatment line that started at or after PFS IRC progression date by the number of progressed patients.

Treatment duration of subsequent treatment was assumed to amount to 6.3 months in both treatment arms, based on data from MajesTEC-1; there was data available from MonumenTAL-1 showing mean duration of subsequent treatment equalling 4.22 months, which would imply shorter treatment duration of subsequent treatment for talquetamab treated patients compared to those treated with teclistamab but this is likely the result of shorter follow-up from MonumenTAL-1 compared to MajesTEC-1 (Janssen 2023c, Janssen 2023e). The distribution of subsequent therapies was assumed to be the same as the physician's choice basket in the teclistamab evaluation, i.e., equal distribution of Kd, PVd, and Pd; physician's choice was the comparator in the evaluation of teclistamab.

Table 38. Pharmaceutical costs of subsequent treatments

Therapy	Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity
Kd	Carfilzomib (IV)	10mg	1	1303.85	100%
	Dexamethasone (oral)	4mg	100	380.1	100%
PVd	Pomalidomide (oral)	4mg	21	52836.61	100%
	Bortezomib (SC)	3.5mg	1	116.4	100%
	Dexamethasone (oral)	4mg	100	380.1	100%
Pd	Pomalidomide (oral)	4mg	21	52836.61	100%
	Dexamethasone (oral)	4mg	100	380.1	100%

Abbreviations: Kd: Carfilzomib+Dexamethasone (oral); PVd: Pomalidomide+Bortezomib+Dexamethasone (oral); Pd: Pomalidomide+ Dexamethasone (oral)

11.7 Patient costs

Patient costs were estimated by the time spent due to administration and visits and transportation costs (round trip). Patient costs were sourced from the DMC's guidance (Medicinrådet 2022 Værdisætning af enhedsomkostninger v.1.7). The costs and resource use applied in the analysis are presented in Table 39.

Table 39. Patient costs used in the model

Activity	Time spent	Unit cost (DKK)
Visit or drug administration	4 hours (per patient)	203 per hour
Round trip		149.2 per round trip

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable. Cost of palliative care was not included based on the Carvykti assessment by DMC.

12. Results

12.1 Base case overview

Table 40 presents an overview of the base case.

Table 40. Base case overview

Feature	Description
Comparator	[redacted]
Type of model	
Time horizon	
Treatment line	
Measurement and valuation of health effects	
Costs included	
Dosage of pharmaceutical	
Average time on treatment	
Parametric function for OS	
Parametric function for PFS	
Inclusion of waste	
Average time in model health state	

12.1.1 Base case results

Table 41 presents total costs, life-years gained, QALYs, and incremental costs per QALY for talquetamab 0.8 mg/kg Q2W versus teclistamab. Compared with teclistamab, talquetamab generated additional 1.11 QALYs and 1.39 life-years with a higher total cost (incremental cost 1,181,359 DKK). The incremental cost per QALY gained was 1,059,729 DKK.

Table 41. Base case results, discounted estimates

	Talquetamab	Teclistamab	Difference
Cost outcome (DKK)			
Total PFS			
Total treatment cost			
Pharmaceutical costs			
Administration			
Follow-up cost			
AEs			
Total non-medical costs			
Travel costs			
Patient time			
Total PPS			
Follow-up cost			
Subsequent treatment cost			
Total non-medical costs			
Travel costs			
Patient time			
Total costs	3,642,259	2,458,687	**1,183,573**
Life years & QALYs			
Life years gained (PFS)			
Life years gained (PPS)			
Total life years			
QALYs (PFS)			
QALYs (PPS)			
QALYs (adverse reactions)			
Total QALYs			

Incremental costs per life year gained: 852,541 DKK
Incremental cost per QALY gained (ICER): 1,062,279 DKK

12.2 Sensitivity analyses

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty.

12.2.1 One-way sensitivity analyses

One-way sensitivity analysis (OWSA) was implemented for the base case. The top ten most impactful parameters on the ICER are shown in the tornado chart (Figure 13) and in Table 42 below.

In the OWSA, each parameter of interest was changed independently while all others remained at their base case values. Parameters with uncertainty were included in the OWSA, including the following key model inputs:

- Patient demographics (i.e., age, weight, body surface area)
- Duration of subsequent treatment and proportion taking subsequent treatment
- Vial sharing
- Frequency of resource utilization and unit costs
- AE rates and unit costs
- Health state utility values

Where possible, CIs or published ranges were used as alternative values. In the absence of CIs or published ranges, upper and lower bounds tested in the OWSA were calculated assuming a standard error (SE) of 10% of the base case value.

Results for the 10 most impactful parameters on the ICER are presented below (Figure 13 and Table 42). Additional OWSA results can be found in the Excel model. The results indicate that the ICER is most sensitive to the PFS utility weight at the last available data point (treatment cycle 15) which was carried forward to the remaining cycles.

Figure 13. Tornado chart, the top ten most impactful parameters on the ICER

Table 42. One-way sensitivity analyses results, the top ten most impactful parameters

Base case	Change (lower – upper bound CI)	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case				
Talq: PPS utility				
Talq: PFS time dependent utility - Time (28 days) - 24				
Tec: PFS time dependent utility - Time (28 days) - 24				
Tec: PPS utility				
Body weight (mean)				
Duration of subsequent treatment - Talquetamab				
% taking subsequent treatment - Talquetamab				
Duration of subsequent treatment - teclistamab				
% taking subsequent treatment - Teclistamab				
Proportion vial sharing				

Abbreviations: Kd: Carfilzomib+Dexamethasone (oral); Pd: Pomalidomide+ Dexamethasone (oral)

12.2.2 Scenario analyses

Table 43 shows the results from scenario analyses. Results were most sensitive to extrapolating the OS curve of the talquetamab arm with the lognormal distribution and adjusting the PFS curve of the talquetamab arm to equal the PFS curve of the teclistamab arm while simutaltanously applying the same hazard ratios to the TTTD curve for the talquetamab arm. Using shorter time horizon also had substantial impact on the ICER. However, overall the results were relatively robust (stable). Using a Weibull function instead of exponential to extrapolate OS which more appropriately fitted the decreasing hazards in talquetamab (discussed in section 8.1.1.1, decreased the ICER as expected. A non-generalised gamma distribution for OS also dcreased the ICER. The base case used the Weibull distribution for PFS and TTTD; the other plausible option was non-generalised gamma (as discussed in section 8.1.1.2. The ICER was relatively insensitive to

the change in PFS/TTTD distribution. Results were relatively sensitive to assuming 0%/100% vial sharing.

Table 43. Scenario analyses

	Change	Incremental benefit (QALYs)	Incremental cost (DKK)	ICER (DKK/QALY)
Base case		[redacted]	1,183,573	1,062,279
Discount rates	Costs 0%, Benefits 0%	[redacted]	[redacted]	[redacted]
Costs and benefits: 3.5% for 1-35 years	Costs 5%, Benefits 5%	[redacted]	[redacted]	[redacted]
	Costs 3.5% Benefits 0%	[redacted]	[redacted]	[redacted]
Overall survival (OS), Weibull talquetamab and lognormal teclistamab	Lognormal for talquetamab	[redacted]	[redacted]	[redacted]
	Gamma for talquetamab	[redacted]	[redacted]	[redacted]
Progression free survival (PFS) and TTTD, lognormal both arms	PFS of talquetamab equal to PFS of teclistamab*	[redacted]	[redacted]	[redacted]
	Loglogistic for talquetamab	[redacted]	[redacted]	[redacted]
TTD (lognormal), PFS (lognormal), and OS (Weibull), Talquetamab	TTTD equal to TTTD of the Teclistamab arm; PFS adjusted with the same HR as applied to TTTD; OS adjusted with the same HR as applied to TTTD**	[redacted]	[redacted]	[redacted]
Time horizon, 35 years	5 years	[redacted]	[redacted]	[redacted]
	15 years	[redacted]	[redacted]	[redacted]
	25 years	[redacted]	[redacted]	[redacted]
Vial sharing, 50%	100%	[redacted]	[redacted]	[redacted]
	75%	[redacted]	[redacted]	[redacted]
	25%	[redacted]	[redacted]	[redacted]
	0%	[redacted]	[redacted]	[redacted]
AE associated disutilities, yes	No	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression free survival.

* The PFS curve of the talquetamab arm was adjusted through the application of hazard ratios, the same hazard ratio was applied on the TTD curve, trying to reduce bias.

** Progression-free and overall survival are presumably affected by the time patients are spending on treatment (talquetamab). The purpose of the adjustment of PFS and OS is trying to reduce bias.

12.2.3 Probabilistic sensitivity analyses

To account for the joint uncertainty of the underlying parameter estimates, a second order stochastic sensitivity analysis was performed. The probabilistic sensitivity analysis (PSA) shows the overall uncertainty of the incremental cost-effectiveness results for talquetamab compared to teclistamab.

For all inputs, when possible, the SE from the data source were used to define parameter uncertainty. Otherwise, when not reported, the SE was assumed to be 10% of the default value. This was assumed to represent a reasonable degree of uncertainty and provided realistic values. The PSA was conducted using 1,000 iterations, where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs, life-years and QALYs. PFS and OS, probabilities, costs and utilities were varied simultaneously and independently of each other. Time horizon, discount rates and other structural choices related to data sources and assumptions on patient pathways were excluded from the PSA since they were not subject to parameter uncertainty.

Parametric distributions were varied using the means and variance-covariance matrices of the parameters. This helped to account for the correlation between parameters. Common distributions used in a PSA are beta, gamma, log-normal, normal, and Dirichlet (Briggs et al. 2012). The beta distribution was confined by the interval 0–1 and was used for health state utility values and percentages/proportions, such as the proportion of patients receiving bridging therapy or undergoing subsequent treatments. The gamma distribution was used for cost inputs as it is confined by the interval 0–∞. The lognormal distribution is a normal distribution on the log scale and was used for sampling HRs as well as counts of resource use. The normal distribution was used for sampling age; weight; body surface area (BSA); and duration of the pre-infusion period, AEs, and conditioning, bridging and subsequent therapies. The Dirichlet distribution is a multivariate generalization of the beta distribution and was used for considering the distribution of probabilities across more than two data categories, such as the distribution of patients on each subsequent therapy.

The mean total costs and QALYs from the PSA were similar to those of the deterministic results. The ICER was also similar between the two analyses. Therefore, the overall conclusion regarding cost effectiveness remained unchanged; treatment with Talquetamab is more costly but also more effective than treatment with teclistamab.

Table 44. PSA results

Comparator	Mean QALY (SD)	Mean Cost (SD)
Talquetamab	[redacted]	
Teclistamab		
Incremental cost and QALY of talquetamab vs teclistamab		

Abbreviations: SD: Standard deviation: PSA: probabilistic sensitivity analysis

Figure 14 presents the cost-effectiveness plane, which shows that a majority of the 10,000 iterations were in the North-East quadrant. This means that talquetamab resulted in more QALYs and higher costs compared to teclistamab.

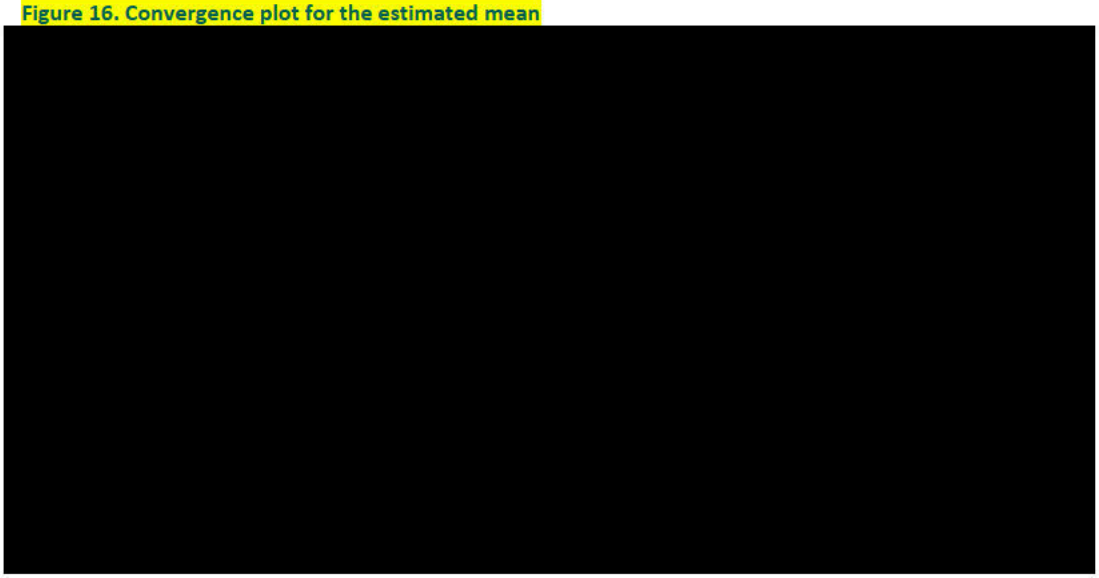
Figure 14. Cost-effectiveness plane (10,000 iterations)

Figure 15 presents the cost-effectiveness acceptability curve (CEAC).

Figure 15. Cost-effectiveness acceptability curve (CEAC)

Figure 16 includes a convergence plot for the estimated mean. This is an iteration plot of ICER as a function of the number of PSA simulations needed for the outputs of interest to be considered to have converged i.e., the mean ICER has stabilised to within the specified accuracy of the deterministic ICER (Hatswell et al. 2018). In this case approximately 1,000-1,500 PSA simulations was needed.

Figure 16. Convergence plot for the estimated mean



13. Budget impact analysis

Based on the prevalence and incidence Janssen Pharmaceuticals is assuming that approximately 12% of the MM patients i.e., 70 patients to be triple-class exposed and eligible for Talquetamab per year. A constant number was assumed over the five-year period of 70 new patients per year. The numbers presented in Table 45 represent the number of patients expected to be treated in a scenario when Talquetamab is introduced and one scenario when Talquetamab is not introduced.

Number of patients (including assumptions of market share)

Table 45. Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	2024	2025	2026	2027	2028
			Recommendation		
Talquetamab	11	18	21	28	28
Teclistamab	59	52	49	42	42
			Non-recommendation		
Talquetamab	0	0	0	0	0
Teclistamab	70	70	70	70	70

Budget impact

Table 46. Expected budget impact of recommending the pharmaceutical for the indication

	2024	2025	2026	2027	2028
The pharmaceutical under consideration is recommended	78,424,729	108,000,371	126,151,183	141,522,003	153,398,186
The pharmaceutical under consideration is NOT recommended	75,249,144	100,288,523	113,765,830	123,482,457	131,150,013
Budget impact of the recommendation	3,175,585	7,711,848	12,385,353	18,039,528	22,248,173

14. List of experts

[redacted]

15. References

Austin, P. C. 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med,* 28**,** 3083-3107.

Austin, P. C. 2014. A comparison of 12 algorithms for matching on the propensity score. *Stat Med,* 33**,** 1057-69.

Bacelar, M., Cooper, C., Hyde, C., Latimer, N. & Murray, D. 2014. *The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171). Single Technology Appraisal NIHR HTA Programme (13/07/01). Matrix and Peninsula Technology Assessment Group 2014.* [Online]. Available: https://www.nice.org.uk/guidance/gid-tag452/documents/multiple-myeloma-lenalidomide-post-bortezomib-part-rev-ta171-evaluation-report2 [Accessed 5 October 2023].

Briggs, A. H., Weinstein, M. C., Fenwick, E. A., Karnon, J., Sculpher, M. J. & Paltiel, A. D. 2012. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making,* 32**,** 722-32.

Burnham, K. P. & Anderson, D. R. 2004. Multimodel Inference:Understanding AIC and BIC in Model Selection. *Sociological Methods & Research,* 33**,** 261-304.

Caers, J., Paiva, B., Zamagni, E., Leleu, X., Bladé, J., Kristinsson, S., Touzeau, C., Abildgaard, N., Terpos, E. & Heusschen, R. 2018. Diagnosis, treatment, and response assessment in solitary plasmacytoma: updated recommendations from a European Expert Panel. *J Hematol Oncol,* 11**,** 10.

Chari, A., Touzeau, C., Schinke, C., Minnema, M. C., Berdeja, J., Oriol, A., Van De Donk, N. W. C. J., Rodriguez-Otero, P., Askari, E., Mateos, M. V., Costa, L. J., Caers, J., Rasche, L., Krishnan, A., Vishwamitra, D., Ma, X., Qin, X., Gries, K. S., Campagna, M., Masterson, T., Hilder, B., Tolbert, J., Renaud, T., Goldberg, J. D., Heuck, C., San-Miguel, J. & Moreau, P. 2022. Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumenTAL-1. ASH 2022.

Clinicaltrials.Gov. 2017. *Dose Escalation Study of Talquetamab in Participants With Relapsed or Refractory Multiple Myeloma* [Online]. Available: https://ClinicalTrials.gov/show/NCT03399799 [Accessed August 5, 2022].

Clinicaltrials.Gov. 2021. *A Study of Talquetamab in Participants With Relapsed or Refractory Multiple Myeloma* [Online]. Available: https://ClinicalTrials.gov/show/NCT04634552 [Accessed August 5, 2022].

Clinicaltrials.Gov. 2024a. *Dose Escalation Study of Teclistamab, a Humanized BCMA*CD3 Bispecific Antibody, in Participants With Relapsed or Refractory Multiple Myeloma (MajesTEC-1)* [Online]. Available: https://clinicaltrials.gov/study/NCT03145181 [Accessed 7 March 2024].

Clinicaltrials.Gov. 2024b. *A Study of Teclistamab in Participants With Relapsed or Refractory Multiple Myeloma (MajesTEC-1)* [Online]. Available: https://clinicaltrials.gov/study/NCT04557098 [Accessed 7 March 2024].

Dansk Myelomatose Studie Gruppe (Dmsg). 2022. *Myelomatose – Relapsbehandling v2.0* [Online]. Available: https://myeloma.hematology.dk/index.php/vejledninger-dmsg/441-relapsbehandling-af-myelomatose-1/file [Accessed 7 July 2023].

Delforge, M., Moreau, P., Einsele, H., De Stefano, V., Lindsey-Hill, J., Vincent, L., Mangiacavali, S., Perrot, A., Ocio, E., Ten Seldam, S., Groen-Damen, E., Semerjian, M., Strulev, V., Schecter, J. M., Roccia, T., Gries, K. S., Nesheiwat, T., Wapenaar, R., Mateos, M. & Weisel, K. 2022. Health-Related Quality of Life in Patients With Relapsed/Refractory Multiple Myeloma Receiving Real-Life Current Standard of

Care in the LocoMMotion Study. Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL, USA & Virtual.

Delgado, A. & Guddati, A. K. 2021. Clinical endpoints in oncology - a primer. *Am J Cancer Res,* 11**,** 1121-1131.

Despiégel, N., Touboul, C., Flinois, A., Saba, G., Suzan, F., Gonzalez-Mcquire, S. & Bonnetain, F. 2019. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. *Clin Lymphoma Myeloma Leuk,* 19**,** e13-e28.

Elsada, A., Zalin-Miller, A., Knott, C. & Caravotas, L. 2021. A registry study of relapsed or refractory multiple myeloma pre-exposed to three or more prior therapies including a proteasome inhibitor, an immunomodulatory agent and CD38-targeted monoclonal antibody therapy in England. *EJHaem,* 2**,** 493-497.

Elze, M. C., Gregson, J., Baber, U., Williamson, E., Sartori, S., Mehran, R., Nichols, M., Stone, G. W. & Pocock, S. J. 2017. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. *J Am Coll Cardiol,* 69**,** 345-357.

Ema. 2023a. *Talvey (talquetamab) - Summary of product characteristics* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/talvey-epar-product-information_en.pdf [Accessed 5 October 2023].

Ema. 2023b. *Talvey (talquetamab), CHMP summary of positive opinion* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/talvey [Accessed 28 August 2023].

Ema. 2023c. *Tecvayli (teclistamab) - Summary of product characteristics* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/talvey-epar-product-information_en.pdf [Accessed 7 March 2023].

European Commission. 2024. *Union Register of medicinal products for human use - Tecvayli* [Online]. Available: https://ec.europa.eu/health/documents/community-register/html/h1675.htm [Accessed 7 March 2024].

Faria, R., Alava, M. H., Manca, A. & Wailoo, A. J. 2015. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data

Gandhi, U. H., Cornell, R. F., Lakshman, A., Gahvari, Z. J., Mcgehee, E., Jagosky, M. H., Gupta, R., Varnado, W., Fiala, M. A., Chhabra, S., Malek, E., Mansour, J., Paul, B., Barnstead, A., Kodali, S., Neppalli, A., Liedtke, M., Narayana, S., Godby, K. N., Kang, Y., Kansagra, A., Umyarova, E., Scott, E. C., Hari, P., Vij, R., Usmani, S. Z., Callander, N. S., Kumar, S. K. & Costa, L. J. 2019. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia,* 33**,** 2266-2275.

Globocan 2018. Multiple myeloma fact sheet. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheet.pdf. Accessed: Feb 2022.

Grambsch, P. M. & Therneau, T. M. 1994. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika,* 81**,** 515-526.

Gregory, T., Cohen, A. D., Costello, C. L., Ali, S. A., Berdeja, J. G., Ostertag, E. M., Martin, C., Shedlock, D. J., Resler, M. L. & Spear, M. A. 2018. Efficacy and safety of P-Bcma-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM). *Blood,* 132**,** 1012.

Haefliger, B., Diels, J., Ghilotti, F., Sliwka, H., Potamianou, A., Bacon, T. & Kellermann, L. 2021. Baseline characteristics and survival outcomes of patients with tri-exposed multiple myeloma in a German registry (EHA EBMT poster on file).

Hari, P., Lin, H. M., Zhu, Y., Berg, D., Richardson, P. G. & Moreau, P. 2018. Healthcare resource utilization with ixazomib or placebo plus lenalidomide-dexamethasone in the randomized, double-blind, phase 3 TOURMALINE-MM1 study in relapsed/refractory multiple myeloma. *J Med Econ,* 21**,** 793-798.

Hatswell, A. J., Bullement, A., Briggs, A., Paulden, M. & Stevenson, M. D. 2018. Probabilistic Sensitivity Analysis in Cost-Effectiveness Models: Determining Model Convergence in Cohort Models. *Pharmacoeconomics,* 36**,** 1421-1426.

Hettle, R., Corbett, M., Hinde, S., Hodgson, R., Jones-Diette, J., Woolacott, N. & Palmer, S. 2017. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess,* 21**,** 1-204.

Huang, B., Tian, L., Talukder, E., Rothenberg, M., Kim, D. H. & Wei, L.-J. 2018. Evaluating Treatment Effect Based on Duration of Response for a Comparative Oncology Study. *JAMA Oncology,* 4**,** 874-876.

Jagannath, S., Joseph, N., He, J., Crivera, C., Fu, A. Z., Garret, A. & Shah, N. 2021. Healthcare Costs Incurred by Patients with Multiple Myeloma Following Triple Class Exposure (TCE) in the US. *Oncol Ther,* 9**,** 659-669.

Janssen 2021. Data on file. Treatment of Mutliple Myeloma (MM), Denmark.

Janssen 2022a. Adjusted comparison of talquetamab in MonumenTAL-1 versus real-world physician's choice in LocoMMotion and MoMMent for the treatment of patients with multiple myeloma with prior exposure to a proteasome inhibitor, an immunomodulatory imide and an anti-CD38 monoclonal antibody. Data-cut 2 final. November 9, 2022. Data on file

Janssen 2022b. Bispecific Core Slide Library Module 6: Key Recent and Emerging Competitors (Updated: August 2022). Data on file.

Janssen 2022c. Efficacy Update to Clinical Study Report Dated 09 November 2022 (Clinical cut-off: September 12, 2022). A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma (MonmenTAL-1). Data on file. .

Janssen 2022d. Efficacy Update to Clinical Study Report Dated 09 November 2022 (Clinical cut-off: September 12, 2022). A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma (MonumenTAL-1). Data on file

Janssen 2022e. Primary Analysis Clinical Study Report (16 May 2022 Cutoff): A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma (MonumenTAL-1; 64407564MMY1001). Date: October 27, 2022. Data on file.

Janssen 2022f. Talquetamab Company Core Data Sheet, 22 November 2022, Version 001. Data on file.

Janssen 2022g. Topline results: Study 64407564MMY1001 (MonumenTAL-1); primary analysis data cut-off May 16, 2022. Date: July 21, 2022. Data on file.

Janssen 2023a. Draft SmPC talquetamab.

Janssen 2023b. Internal Janssen medical advisor, hematology. *Data on file*.

Janssen 2023c. MajesTEC-1 CSR Jan 2023 data-cut. *Data on file*.

Janssen 2023d. MMY4001 Interim Analysis Final 11MAY2023 - LocoMMotion Data cut on 27OCT2022.

Janssen 2023e. MonumenTAL-1 CSR Jan 2023 data-cut. *Data on file*.

Janssen 2023f. Pooled LocoMMotion (data-cut October 2022) and MoMMent (data-cut March 2023) CSR, data on file.

Janssen 2023g. Unanchored matching-adjusted indirect comparison (MAIC) to evaluate the comparative treatment efficacy of talquetamab in MonumenTAL-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with multiple myeloma with prior exposure to a proteasome inhibitor, an immunomodulatory imide drug and an anti-CD38 monoclonal antibody. MAIC Report. Data-cut 3 Final. 23 June 2023. Data on file.

Janssen 2023h. Update to Clinical Study Reports Dated 09 November 2022 and 14 November 2022. A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma. MonumenTAL-1. Data-cut: 17 January 2023. Approved. Date: 22 June 2023.

Jensen, M. B., Jensen, C. E., Gudex, C., Pedersen, K. M., Sorensen, S. S. & Ehlers, L. H. 2023. Danish population health measured by the EQ-5D-5L. *Scand J Public Health,* 51**,** 241-249.

Kamal, M., Wang, X. S., Shi, Q., Zyczynski, T. M., Davis, C., Williams, L. A., Lin, H. K., Garcia-Gonzalez, A., Cleeland, C. S. & Orlowski, R. 2021. Symptom burden and its functional impact in patients with "symptomatic" relapsed or refractory multiple myeloma. *Support Care Cancer,* 29**,** 467-475.

Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Bladé, J., Mateos, M. V., Dimopoulos, M., Kastritis, E., Boccadoro, M., Orlowski, R., Goldschmidt, H., Spencer, A., Hou, J., Chng, W. J., Usmani, S. Z., Zamagni, E., Shimizu, K., Jagannath, S., Johnsen, H. E., Terpos, E., Reiman, A., Kyle, R. A., Sonneveld, P., Richardson, P. G., Mccarthy, P., Ludwig, H., Chen, W., Cavo, M., Harousseau, J. L., Lentzsch, S., Hillengass, J., Palumbo, A., Orfao, A., Rajkumar, S. V., Miguel, J. S. & Avet-Loiseau, H. 2016. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol,* 17**,** e328-e346.

Kumar, S. K., Dispenzieri, A., Lacy, M. Q., Gertz, M. A., Buadi, F. K., Pandey, S., Kapoor, P., Dingli, D., Hayman, S. R., Leung, N., Lust, J., Mccurdy, A., Russell, S. J., Zeldenrust, S. R., Kyle, R. A. & Rajkumar, S. V. 2014. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia,* 28**,** 1122-1128.

Kurtin, S., Lilleby, K. & Spong, J. 2013. Caregivers of multiple myeloma survivors. *Clin J Oncol Nurs,* 17 Suppl**,** 25-32.

Kyle, R. A. & Rajkumar, S. V. 2009. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia,* 23**,** 3-9.

Latimer, N. 2011. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data.

Launois, R., Reboul-Marty, J., Henry, B. & Bonneterre, J. 1996. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. *Pharmacoeconomics,* 10**,** 504-21.

Lee, D. W., Gardner, R., Porter, D. L., Louis, C. U., Ahmed, N., Jensen, M., Grupp, S. A. & Mackall, C. L. 2014. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood,* 124**,** 188-195.

Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., Maus, M. V., Park, J. H., Mead, E., Pavletic, S., Go, W. Y., Eldjerou, L., Gardner, R. A., Frey, N., Curran, K. J., Peggs, K., Pasquini, M., Dipersio, J. F., Van Den Brink, M. R. M., Komanduri, K. V., Grupp, S. A. & Neelapu, S. S. 2019. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Blood Marrow Transplant,* 25**,** 625-638.

Li, F., Morgan, K. L. & Zaslavsky, A. M. 2018. Balancing covariates via propensity score weighting. *J Am Stat Assoc,* 113**,** 390-400.

Lloyd, A., Nafees, B., Narewska, J., Dewilde, S. & Watkins, J. 2006. Health state utilities for metastatic breast cancer. *Br J Cancer,* 95**,** 683-90.

Lokhorst, H. M., Van Der Holt, B., Zweegman, S., Vellenga, E., Croockewit, S., Van Oers, M. H., Von Dem Borne, P., Wijermans, P., Schaafsma, R. & De Weerdt, O. 2010. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood, The Journal of the American Society of Hematology,* 115**,** 1113-1120.

Ludwig, H., Pönisch, W., Knop, S., Egle, A., Hinke, A., Schreder, M., Lechner, D., Hajek, R., Gunsilius, E., Petzer, A., Weisel, K., Niederwieser, D., Einsele, H., Willenbacher, W., Rumpold, H., Pour, L., Jelinek, T., Krenosz, K. J., Meckl, A., Nolte, S., Melchardt, T., Greil, R. & Zojer, N. 2020. Quality of life in patients with relapsed/refractory multiple myeloma during ixazomib-thalidomide-dexamethasone induction and ixazomib maintenance therapy and comparison to the general population. *Leuk Lymphoma,* 61**,** 377-386.

Macewan, J. P., Batt, K., Yin, W., Peneva, D., Sison, S., Vine, S. & Chen, C. 2018. Economic burden of multiple myeloma among patients in successive lines of therapy in the United States. *Leuk Lymphoma,* 59**,** 941-949.

Madduri, D., Hagiwara, M., Parikh, K., Pelletier, C., Delea, T. E., Kee, A. & Chari, A. 2021. Real-world treatment patterns, healthcare use and costs in triple-class exposed relapsed and refractory multiple myeloma patients in the USA. *Future Oncol,* 17**,** 503-515.

Martin, T., Iii, Lin, Y., Agha, M., Cohen, A. D., Htut, M., Stewart, A. K., Hari, P., Berdeja, J. G., Madduri, D., Usmani, S. Z., Yeh, T.-M., Allred, A. J., Olyslager, Y., Banerjee, A., Goldberg, J. D., Schecter, J. M., Jackson, C. C., Deraedt, W., Gries, K. S., Fastenau, J., Wu, X., Carrasco, M. J., Akram, M., Hossain, F., Jakubowiak, A. & Jagannath, S. 2020. Health-Related Quality of Life in the Cartitude-1 Study of Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma. *Blood,* 136**,** 41-42.

Mateos, M.-V., Weisel, K., De Stefano, V., Goldschmidt, H., Delforge, M., Mohty, M., Cavo, M., Vij, R., Lindsey-Hill, J., Dytfeld, D., Angelucci, E., Perrot, A., Benjamin, R., Van De Donk, N. W. C. J., Ocio, E. M., Scheid, C., Gay, F., Roeloffzen, W., Rodriguez-Otero, P., Broijl, A., Potamianou, A., Sakabedoyan, C., Semerjian, M., Keim, S., Strulev, V., Schecter, J. M., Vogel, M., Wapenaar, R., Nesheiwat, T., San-Miguel, J., Sonneveld, P., Einsele, H. & Moreau, P. 2022a. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia,* 36**,** 1371-1376.

Mateos, M. V., Weisel, K., De Stefano, V., Goldschmidt, H., Delforge, M., Mohty, M., Cavo, M., Vij, R., Lindsey-Hill, J., Dytfeld, D., Angelucci, E., Perrot, A., Benjamin, R., Van De Donk, N., Ocio, E. M., Scheid, C., Gay, F., Roeloffzen, W., Rodriguez-Otero, P., Broijl, A., Potamianou, A., Sakabedoyan, C., Semerjian, M., Keim, S., Strulev, V., Schecter, J. M., Vogel, M., Wapenaar, R., Nesheiwat, T., San-Miguel, J., Sonneveld, P., Einsele, H. & Moreau, P. 2022b. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia*.

Mathur, M. B., Ding, P., Riddell, C. A. & Vanderweele, T. J. 2018. Web Site and R Package for Computing E-values. *Epidemiology,* 29**,** e45-e47.

Medicinrådet. 2020. *Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose) - version 1.2* [Online]. Available: https://medicinraadet.dk/media/1svpo21c/baggrund-for-medicinraadets-

behandlingsvejledning-vedr-knoglemarvskraeft-myelomatose-vers-12_adlegacy.pdf [Accessed 7 July 2023].

Medicinrådet. 2021. *The Danish Medicines Council methods guide for assessing new pharmaceuticals* [Online]. Available: https://medicinraadet.dk/media/5eibukbr/the-danish-medicines-council-methods-guide-for-assessing-new-pharmaceuticals-version-1-3.pdf [Accessed 5 October 2023].

Medicinrådet. 2023a. *Appendiks: Aldersjustering for sundhedsrelateret livskvalitet* [Online]. Available: https://medicinraadet.dk/media/mbtgpjjl/efter-1-januar-2021-appendiks-til-medicinr%C3%A5dets-metodevejledning-aldersjustering-adlegacy.pdf [Accessed 5 October 2023].

Medicinrådet. 2023b. *Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose) - version 1.10* [Online]. Available: https://medicinraadet.dk/anbefalinger-og-vejledninger/behandlingsvejledninger-og-laegemiddelrekommandationer/knoglemarvskraeft-myelomatose [Accessed 15 September 2023].

Medicinrådet. 2024. *Teclistamab (Tecvayli)* [Online]. Available: https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/t/teclistamab-tecvayli-knoglemarvskraeft [Accessed 7 March 2024].

Mehra, M., Vogel, M., Valluri, S., Nair, S., Schecter, J., Jagannath, S., Weisel, K. & Usmani, S. Z. 2020. Patient characteristics and treatment patterns in relapsed/refractory multiple myeloma patients after exposure to a proteasome inhibitor, an immunomodulatory agent and daratumumab. *J Clin Oncol,* 38**,** e20540-e20540.

Moreau, P., Attal, M. & Facon, T. 2015. Frontline therapy of multiple myeloma. *Blood,* 125**,** 3076-3084.

Moreau, P., Garfall, A. L., Van De Donk, N., Nahi, H., San-Miguel, J. F., Oriol, A., Nooka, A. K., Martin, T., Rosinol, L., Chari, A., Karlin, L., Benboubker, L., Mateos, M. V., Bahlis, N., Popat, R., Besemer, B., Martinez-Lopez, J., Sidana, S., Delforge, M., Pei, L., Trancucci, D., Verona, R., Girgis, S., Lin, S. X. W., Olyslager, Y., Jaffe, M., Uhlar, C., Stephenson, T., Van Rampelbergh, R., Banerjee, A., Goldberg, J. D., Kobos, R., Krishnan, A. & Usmani, S. Z. 2022. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med,* 387**,** 495-505.

National Comprehensive Cancer Network *NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 5.2022* [Online]. Available: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1445 [Accessed September 9, 2022].

National Institute for Health and Care Excellence (Nice). 2018. *Single Technology Appraisal daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933] Committee Papers* [Online]. Available: https://www.nice.org.uk/guidance/ta783/evidence [Accessed 27 March 2024].

National Institute for Health and Care Excellence (Nice). 2019a. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies - Technology appraisal guidance [TA559]* [Online]. Available: https://www.nice.org.uk/guidance/ta559 [Accessed 5 October 2023].

National Institute for Health and Care Excellence (Nice). 2019b. *Position statement on use of the EQ-5D-5L value set for England (updated October 2019)* [Online]. Available: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l [Accessed 5 October 2023].

National Institute for Health and Care Excellence (Nice). 2023. *Single Technology Appraisal Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057] Committee Papers* [Online]. Available: https://www.nice.org.uk/guidance/ta897/history [Accessed 27 March 2024].

Nordcan 2.0. 2022. *Total prevalence for MM in Denmark (2014-2019)* [Online]. Available: https://nordcan.iarc.fr/en/dataviz/prevalence?cancers=380&sexes=1_2&populations=208&mode=cancer&multiple_populations=0&multiple_cancers=1&years=2014_2019&years_available=1943_2020&key=total&survival=0. [Accessed].

Nordcan 2.0. 2023a. *Incidence of multiple myeloma, absolute numbers, both sexes (2016-2021)* [Online]. Available: https://nordcan.iarc.fr/en/dataviz/trends?cancers=380&sexes=0&populations=208&mode=cancer&multiple_populations=0&multiple_cancers=1&years=2016_2021&years_available=1943_2021&key=total [Accessed 5 October 2023].

Nordcan 2.0. 2023b. *Total prevalence for MM in Denmark (2016-2021)* [Online]. Available: https://nordcan.iarc.fr/en/dataviz/prevalence?mode=cancer&group_populations=1&multiple_cancers=1&cancers=380&sexes=0&group_cancers=0&key=total&survival=0&populations=208&years=2016_2021 [Accessed 5 October 2023].

Ossa, D. F., Briggs, A., Mcintosh, E., Cowell, W., Littlewood, T. & Sculpher, M. 2007. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. *Pharmacoeconomics,* 25**,** 223-37.

Rajkumar, S. V., Harousseau, J.-L., Durie, B., Anderson, K. C., Dimopoulos, M., Kyle, R., Blade, J., Richardson, P., Orlowski, R. & Siegel, D. 2011. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood, The Journal of the American Society of Hematology,* 117**,** 4691-4695.

Ramsenthaler, C., Osborne, T. R., Gao, W., Siegert, R. J., Edmonds, P. M., Schey, S. A. & Higginson, I. J. 2016. The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. *BMC Cancer,* 16**,** 427.

Rasche, L., Schinke, C., Chari, A., Lipe, B., Lavi, N., Rodriguez-Otero, P., Vishwamitra, D., Skerget, S., Verona, R., Ma, X., Khedkar, S., Hilder, B., Masterson, T., Campagna, M., Renaud, T., Tolbert, J., Heuck, C., Smit, D. & Van De Donk, N. 2023. Analysis of Infections and Parameters of Humoral Immunity in Patients With Relapsed/Refractory Multiple Myeloma Treated With Talquetamab Monotherapy in MonumenTAL-1. Presented at EHA 2023 Hybrid Congress; June 8-11, 2023; Frankfurt, Germany. .

Rizzo, M., Xu, Y., Panjabi, S. & Iheanacho, I. 2014. A Systematic Literature Review of the Humanistic Burden of Multiple Myeloma. *Value Health,* 17**,** A537.

Rosenbaum, P. R. & Rubin, D. B. 1983. The central role of the propensity score in observational studies for causal effects. *Biometrika,* 70**,** 41-55.

Rosinol, L., Beksac, M., Zamagni, E., Van De Donk, N., Anderson, K. C., Badros, A., Caers, J., Cavo, M., Dimopoulos, M. A., Dispenzieri, A., Einsele, H., Engelhardt, M., Fernandez De Larrea, C., Gahrton, G., Gay, F., Hajek, R., Hungria, V., Jurczyszyn, A., Kroger, N., Kyle, R. A., Leal Da Costa, F., Leleu, X., Lentzsch, S., Mateos, M. V., Merlini, G., Mohty, M., Moreau, P., Rasche, L., Reece, D., Sezer, O., Sonneveld, P., Usmani, S. Z., Vanderkerken, K., Vesole, D. H., Waage, A., Zweegman, S., Richardson, P. G. & Blade, J. 2021. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. *Br J Haematol,* 194**,** 496-507.

Schinke, C., Touzeau, C., Minnema, M. C., Van De Donk, N., Rodrigo-Otero, P., Mateos, M., Rasche, L., Ye, J. C., Vishwamitra, D., Ma, X., Qin, X., Campagna, M., Masterson,

T., Hilder, B., Tolbert, J., Renaud, T., Goldberg, J., Heuck, C. & Chari, A. 2023. Pivotal Phase 2 MonumenTAL-1 Results of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, for Relapsed/Refractory Multiple Myeloma. Presented at 2023 ASCO Annual Meeting. June 2-6, 2023; Chicago, IL, US & Virtual.

Smith-Palmer, J., Bae, J. P., Boye, K. S., Norrbacka, K., Hunt, B. & Valentine, W. J. 2016. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. *Clinicoecon Outcomes Res,* 8**,** 559-571.

Statistics Denmark. 2023. *Life table 2021-2022* [Online]. Available: https://statistikbanken.dk/statbank5a/SelectVarVal/Define.asp?Maintable=HISB8&PLanguage=1 [Accessed 5 October 2023].

Sundhedsdatastyrelsen. 2023. *Interaktiv DRG* [Online]. Available: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/gruppering-drg/interaktiv-drg [Accessed 5 October 2023].

Terpos, E., Katodritou, E., De La Rubia, J., Hungria, V., Hulin, C., Roussou, M., Delforge, M., Bries, G., Stoppa, A. M., Aagesen, J., Sargin, D., Belch, A., Ahlberg, L., Diels, J., Olie, R. A., Robinson, D., Jr., Spencer, M., Potamianou, A., Van De Velde, H. & Dimopoulos, M. A. 2018. Bortezomib-based therapy for relapsed/refractory multiple myeloma in real-world medical practice. *Eur J Haematol,* 101**,** 556-565.

Tolley, K., Goad, C., Yi, Y., Maroudas, P., Haiderali, A. & Thompson, G. 2013. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ,* 14**,** 749-59.

Vanderweele, T. J. 2019. Principles of confounder selection. *Eur J Epidemiol,* 34**,** 211-219.

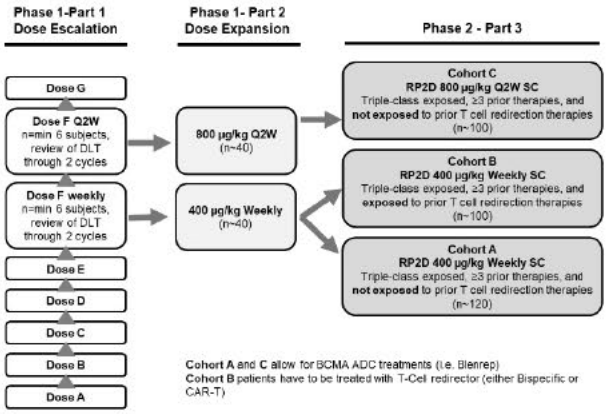
Vanderweele, T. J. & Ding, P. 2017. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med,* 167**,** 268-274.

Weisel, K., Martin, T., Yong, K., Qi, K., Londhe, A., Kobos, R., Qi, M., Schecter, J., Vogel, M., Valluri, S., Krishna, S. G. & Jagannath, S. 2021. Characteristics and Treatment Patterns of Triple-Class Exposed Patients With Relapsed/Refractory Multiple Myeloma Who Participated in Clinical Trials of Daratumumab. (Presented at 47th annual EBMT meeting) (data on file).

Zhao, L., Claggett, B., Tian, L., Uno, H., Pfeffer, M. A., Solomon, S. D., Trippa, L. & Wei, L. 2016. On the restricted mean survival time curve in survival analysis. *Biometrics,* 72**,** 215-221.

Appendix A. Main characteristics of studies included

Table 47. Main characteristic of studies included – MonumenTAL-1

Trial name: MonumenTAL-1	**NCT number: NCT02299799, NCT04634552**
Objective	The purpose of this study is to evaluate the efficacy of talquetamab in participants with relapsed or refractory multiple myeloma at the recommended Phase 2 dose(s) (RP2Ds) (Part 3)
Publications – title, author, journal, year	N/A
Study type and design	MomumenTAL-1 (NCT03399799 for Phase 1; NCT04634552 for Phase 2) is an ongoing, first-in-human, Phase 1/2, open-label, multicenter clinical trial evaluating the safety, tolerability, pharmacokinetics, and anti-myeloma activity of talquetamab in the treatment of adult patients with triple-class exposed multiple myeloma. Study design: 
Sample size (n)	*320*
Main inclusion criteria	Adult patients (≥18 years) with a documented initial diagnosis of MM according to IMWG diagnostic criteria MM must be measurable by central laboratory assessment Prior treatment: • Cohorts A and C[b]: had received ≥3 prior LOTs, including at least one IMiD, one PI, and an anti-CD38 mAb (TCE); no exposure to T cell redirection therapies • Cohort B: had received ≥3 prior LOTs, including at least one IMiD, one PI, and an anti-CD38 mAb (TCE), as well as exposure to T cell redirection therapies

Trial name: MonumenTAL-1	NCT number: NCT02299799, NCT04634552
	Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1 (Phase 1) or 0 to 2 (Phase 2) Women of childbearing potential must have a negative pregnancy test at screening and prior to the first dose of study drug using a highly sensitive pregnancy test either serum (beta human chorionic gonadotropin [hCG]) or urine
Main exclusion criteria	For Cohorts A and C: exposure to a CAR-T or T cell redirection therapy at any time For Cohort B: exposure to T cell redirection therapy within 3 months Any prior GPRC5D targeting therapy Vaccinated with live, attenuated vaccine within 4 weeks or as recommended by the product manufacturer prior to the first dose, during treatment, or within 100 days of the last dose of talquetamab Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less, except for alopecia or peripheral neuropathy Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug (does not include pretreatment medication) Stroke or seizure within 6 months prior to signing the ICF
Intervention	Part 1 (dose escalation; Phase 1): to characterize the safety of talquetamab and to identify the recommended Phase 2 doses (RP2Ds). Part 2 (dose expansion; Phase 1): to further characterize the safety of talquetamab at the putative RP2Ds. Part 3 (dose expansion; Phase 2): to evaluate the efficacy of talquetamab at the RP2Ds in cohorts of TCE patients with RRMM who previously received ≥3 prior lines of therapy (LOT). • Cohort C: 0.8 mg/kg Q2W (n=145)
Comparator(s)	N/A
Follow-up time	This study consists 3 periods: screening phase (up to 28 days), treatment phase (start of study drug administration and continues until the completion of the end of treatment [EOT (30 days (+ 7 days)] visit); and a post-treatment follow-up phase (until the end of study unless the participant has died, is lost to follow up or has withdrawn consent). Total duration of study is up to 2 years (after the last participant receives their first dose) Median duration of follow-up: 11.0 months (range: 0.5 to 26.1).

Trial name: MonumenTAL-1	NCT number: NCT02299799, NCT04634552
	Among 104 responders, the median duration of follow-up was 11.2 months (range: 2.7 to 26.1); 94.2% and 83 79.8% of responders had at least 6 and 9 months of follow-up, respectively. The median duration of talquetamab treatment was 6.9 months (range: <0.1 to 25.3).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary endpoint:** • Overall response rate (ORR) **Secondary endpoints:** • Duration of response (DOR) • Very good partial response (VGPR) or better rate • Complete response (CR) or better rate • Stringent complete response (sCR) rate • Time to response (TTR) • Time to Next Treatment (TTNT) • Progression-free survival (PFS) • Overall survival (OS) • Minimal residual disease (MRD) negative rate • Number of participants with Adverse Events (AEs) • Number of Participants with Serious Adverse Events (SAEs) • Number of Participants with AEs by Severity • Change from Baseline in Health-Related Quality of Life (HRQoL) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) • Change from Baseline in HRQoL as Assessed by EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L) **Other endpoints (results not included in this application):** • Number of Participants with Abnormalities in Clinical Laboratory Values • Serum Concentration of Talquetamab • Number of Participants with Talquetamab Antibodies • Change from Baseline in HRQoL as Assessed by Patient Global Impression of Severity (PGIS) • Overall Response Rate (ORR) in Participants with High-risk Molecular Features
Method of analysis	All analyses were based on participants from the All Treated Analysis Set. As the study was single arm, no between group-analyses were performed.

Trial name: MonumenTAL-1	NCT number: NCT02299799, NCT04634552
Subgroup analyses	Subgroup analyses were performed for: • Sex (Male/Female) • Age (<65 years, 65 - <75 years, ≥75 years) • Baseline renal function (≤60 mL/min/1.73m², >60 mL/min/1.73m²) • Race (White, African American/Black, Other) • Baseline ECOG performance score (0, ≥1)
Other relevant information	

Abbreviations: AE, Adverse Event; CAR-T, chimeric antigen receptor T-cell therapy; CD38, Cluster of Differentiation 38; CR, Complete Response; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Organizatio for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, End of treatment; EQ-5D-5L, EuroQol Five Dimension Five Level Questionnaire, Five Dimension, Five Level; GPRC5D, G protein-coupled receptor family C group 5-member D; hCG, human chorionic gonadotropin; HRQoL, Health Related Quality of Life; ICF, Informed consent form; IMID, Immunomodulatory Drug; IMWG, International Myeloma Working Group; LOT, Line(s) of therapy; MM, Multiple Myeloma; MRD, Minimal Residual Disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-free Survival; PFS2, Time to progression on the next line of subsequent antimyeloma therapy or death; PGIS, Patient Global Impression of Severity; PI, Proteasome Inhibitor; PS, Propensity score; Q1W, weekly; Q2W, every two weeks; RP2D, Recommended Phase 2 dose; RRMM, Relapsed and/or Refractory Multiple Myeloma;; SAE, Serious Adverse Event; SC, Subcutaneous; sCR, Stringent Complete Response; SOC, Standard of Care; TCE, Triple class exposed; TTNT, Time to Next Treatment; TTR, Time To Response; VGPR, Very Good Partial Response

Table 48. Main characteristic of studies included – MajesTEC-1

Trial name: MajesTEC-1	NCT number: NCT03145181, NCT04557098
Objective	The purpose of this study is to evaluate the efficacy of teclistamab in participants with relapsed or refractory multiple myeloma at the recommended Phase 2 dose(s) (RP2Ds) (Part 3)
Publications – title, author, journal, year	N/A
Study type and design	MajesTEC-1 (NCT03145181 for Phase 1; NCT04557098 for Phase 2) is an ongoing, first-in-human, Phase 1/2, open label, multicenter clinical trial evaluating the safety, tolerability, pharmacokinetics, and anti-myeloma activity of talquetamab in the treatment of adult patients with triple class exposed multiple myeloma. Study design:

Trial name: MajesTEC-1	NCT number: NCT03145181, NCT04557098
	• Part 1 (Phase 1, Dose Escalation): To identify the proposed recommended Phase 2 dose(s) and schedule assessed to be safe for teclistamab. • Part 2 (Phase 1, Dose Expansion): To characterize the safety and tolerability of teclistamab at the proposed recommended Phase 2 dose(s). • Part 3 (Phase 2): To evaluate the efficacy of teclistamab at the proposed recommended Phase 2 dose(s)
Sample size (n)	*165*
Main inclusion criteria	Age ≥18 years with documented diagnosis of MM according to IMWG diagnostic criteria, Measurable disease: MM must be measurable by central laboratory assessment: • Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or, • Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio, • If central laboratory assessments are not available, relevant local laboratory measurements must exceed the minimum required level by at least 25%, Prior treatment: • Cohort A: received ≥3 prior MM treatment lines of treatment and previously received an ImiD, PI, and anti-CD38 mAb, • Cohort B: received ≥4 prior lines of treatment and whose disease is penta-drug refractory to an anti-CD38 mAb, ≥2 Pis, ≥2 ImiDs (refractory multiple myeloma as defined by IMWG consensus criteria)[a], • Cohort C: received ≥3 prior lines of treatment that included a PI, an ImiD, an anti-CD38 mAb, and an anti-BCMA treatment (with CART-T cells or an ADC), ECOG Performance Status score of 0 or 1, Pretreatment clinical laboratory values meeting minimal thresholds defined by the protocol[b].
Main exclusion criteria	Plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome, or primary amyloid light-chain amyloidosis,

Trial name: MajesTEC-1	NCT number: NCT03145181, NCT04557098
	Received any therapy that is targeted to BCMA, except for Cohort C, Toxicities from previous anticancer therapies that have not resolved to baseline or to ≤ grade 1, Known active CNS involvement or exhibits clinical signs of meningeal involvement of MM, Myelodysplastic syndrome or active malignancies other than RRMM, except: • Non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured, • Skin cancer treated within the last 24 months that is considered completely cured, • Noninvasive cervical cancer treated within the last 24 months that is considered completely cured, • Localized prostate cancer, • Breast cancer: Adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence, • Malignancy that is considered cured with minimal risk of recurrence, Prior allogenic stem cell transplant ≤6 months, Prior autologous stem cell transplant ≤12 weeks, Certain medical conditions.
Intervention	Part 1 (dose escalation; Phase 1): to characterize the safety of teclistamab and to identify the recommended Phase 2 doses (RP2Ds). Part 2 (dose expansion; Phase 1): to further characterize the safety of teclistamab at the putative RP2Ds. Part 3 (dose expansion; Phase 2): to evaluate the efficacy of teclistamab at the RP2Ds in cohorts of TCE patients with RRMM who previously received ≥3 prior lines of therapy (LOT).
Comparator(s)	N/A
Follow-up time	This study consists 3 periods: screening phase (up to 28 days), treatment phase (start of study drug administration and continues until the completion of the end of treatment [EOT (30 days (+ 7 days)] visit); and a post-treatment follow-up phase (until the end of study unless the participant has died, is lost to follow up or has withdrawn consent). Total duration of study is up to 2 years (after the last participant receives their first dose)

Trial name: MajesTEC-1	NCT number: NCT03145181, NCT04557098
	Median duration of follow-up: 22.8 months (range: 0.3 to 33.6). The median duration of teclistamab treatment was 9.3 months (range: 0.2 to 33.6).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary endpoint:** • Overall response rate (ORR) **Secondary endpoints:** • Duration of response (DOR) • Very good partial response (VGPR) or better rate • Complete response (CR) or better rate • Stringent complete response (sCR) rate • Time to response (TTR) • Time to Next Treatment (TTNT) • Progression-free survival (PFS) • Overall survival (OS) • Minimal residual disease (MRD) negative rate • Number of participants with Adverse Events (AEs) • Number of Participants with Serious Adverse Events (SAEs) • Number of Participants with AEs by Severity • Change from Baseline in Health-Related Quality of Life (HRQoL) as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) • Change from Baseline in HRQoL as Assessed by EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L) **Other endpoints (results not included in this application):** • Number of Participants with Abnormalities in Clinical Laboratory Values • Serum Concentration of Talquetamab • Number of Participants with Talquetamab Antibodies • Change from Baseline in HRQoL as Assessed by Patient Global Impression of Severity (PGIS) Overall Response Rate (ORR) in Participants with High-risk Molecular Features
Method of analysis	N/A
Subgroup analyses	Subgroup analyses are not presented in this application

Trial name: MajesTEC-1	NCT number: NCT03145181, NCT04557098

Other relevant information	N/A

a Per Protocol Amendment 11, Cohort B was not opened for enrollment as penta-drug refractory patients were enrolled in Cohort A.
b These thresholds are defined in the full inclusion/exclusion criteria.
Abbreviations: AE, Adverse Event; CBR, Clinical benefit rate; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol Five Dimension Five Level Questionnaire, Five Dimension, Five Level; HRQoL, Health Related Quality of Life; IMID, Immunomodulatory Drug; IMWG, International Myeloma Working Group; MRD, Minimal Residual Disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-free Survival; PFS2, Time to progression on the next line of subsequent antimyeloma therapy or death; PI, Proteasome Inhibitor; PRO, Patient reported outcome; RRMM, Relapsed and/or Refractory Multiple Myeloma; sCR, Stringent Complete Response; SOC, Standard of Care; TTNT, Time to Next Treatment; TTR, Time To Response; VGPR, Very Good Partial Response.

Appendix B. Efficacy results per study

B.1 Results per study – MonumenTAL-1

Table 49. Results per study – MonumenTAL-1

				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		
ORR, %				N/A	N/A	N/A	N/A	N/A	N/A	ORR was adjudicated by an IRC	(Janssen 2023e)
	Talquetamab 0.8 mg/kg Q2W	145	71.7% (63.7, 78.9)								
CR or better, %				N/A	N/A	N/A	N/A	N/A	N/A	CR and sCR were adjudicated by an IRC	(Janssen 2023e)
	Talquetamab 0.8 mg/kg Q2W	145	38.6% (30.7, 47.1)								
				N/A	N/A	N/A	N/A	N/A	N/A		

				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**		
VGPR or better, %	Talquetamab 0.8 mg/kg Q2W	145	60.7% (52.2, 68.7)							VGPR or better rate was adjudicated by an IRC	(Janssen 2023e)
DOR, months (median)	Talquetamab 0.8 mg/kg Q2W	145	NE (13.0, NE)	N/A	N/A	N/A	N/A	N/A	N/A	Participants who had not progressed and were alive at the data cut-off, were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy or at the last follow-up date, whichever occurred first.	(Janssen 2023e)
PFS, months (median)	Talquetamab 0.8 mg/kg Q2W	145	14.2(9.6, NE)	N/A	N/A	N/A	N/A	N/A	N/A	PFS was adjudicated by an IRC	(Janssen 2023e)
				N/A	N/A	N/A	N/A	N/A	N/A		

				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**		
TTNT, months (median)	Talquetamab 0.8 mg/kg Q2W	145	16.3 (11.2, 18.6)							Participants who were still alive and did not initiate a next therapy line at time of data-cut were censored at last date known to be alive.	(Janssen 2023e)
OS, months (median)	Talquetamab 0.8 mg/kg Q2W	145	NE (20.1, NE)	N/A	N/A	N/A	N/A	N/A	N/A	Participants still alive or the vital status was unknown were censored at the date last known to be alive.	(Janssen 2023e)

Abbreviations: CI, Confidence Interval; CR, Complete Response; DOR, Duration of Response; IRC, Independent Review Committee; NE, not evaluable; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-free Survival; Q1W, weekly; Q2W, every two weeks; TTNT, Time to Next Treatment; VGPR, Very Good Partial Response

B.1.1 Efficacy and Safety Results for RP2D at 0.8 mg/kg Q2W (Phase 1 and Phase 2 Cohort C)

B.1.1.1 Overview

Efficacy results for talquetamab 0.8 mg/kg Q2W in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C) are available for three clinical cut-offs (Janssen 2022e, Janssen 2022c, Janssen 2023e):

- **Protocol-specified primary analysis with a clinical cut-off of May 16, 2022:**
  - Population: patients from Phase 1 and 2 (N = 145; Phase 1: 36, Phase 2 Cohort C: 109; All Treated Analysis Set) who had no prior exposure to T cell redirection therapies and were treated with talquetamab at the RP2D of 0.8 mg/kg Q2W SC.
  - Median duration of follow-up: 5.1 months (range: 0.2 to 17.9).
  - The median treatment duration of talquetamab treatment was 3.7 months (range: <0.1 to 17.9 months).
    - Talquetamab was administered for at least 6 months in 18.6% of patients and for at least 9 months in 6.9%.
  - Ninety-one (62.8%) patients remained on treatment at the time of the clinical cut-off; 54 (37.2%) discontinued treatment (33 [22.8%] due to PD, 4 [2.8%] due to physician decision, 9 [6.2%] due to an AE, 3 [2.1%] withdrew from/refused further doses, 5 [3.4%] died).
  - At the time of the clinical cut-off, 25 (17.2%) patients had discontinued study participation, (18 [12.4%] died, 4 [2.8%] withdrew consent, 1 [0.7%] were lost to follow-up)
  - At the RP2D of 0.8 mg/kg Q2W SC, the median relative dose intensity (ie, actual vs. prescribed doses), was 99.9% in Cycle 1 and 90.3% in Cycle 2+ of treatment; the median relative dose intensity for all treatment, including step-up doses, was 90.4% at this RP2D.
- **Efficacy update with a clinical cut-off of September 12, 2022**:
  - All Treated Analysis Set: efficacy analysis included 145 patients (Phase 1: 36; Phase 2 Cohort C: 109) who were treated with talquetamab at the RP2D of 0.8 mg/kg Q2W SC.
  - Median duration of follow-up was 8.6 months (range: 0.2 to 22.5 months); among TCE with at least 4 prior LOTs, median follow-up was 8.3 months (range: 0.2 to 22.5).
    - Among responders, the median follow-up was 8.8 months (range: 4.1 to 22.5), and 79.2% and 45.3% of responders had at least 6 and 9 months of follow-up, respectively.
    - Compared with the primary analysis, median follow-up among responders was 2.8 months longer overall.
  - The median treatment duration of talquetamab treatment was 5.8 months (range: <0.1 to 21.6).
  - Thirty-three patients (22.8%) discontinued study participation (26 [17.9%] died [1 due to COVID-19], 4 [2.8%] withdrew consent, and 1 [0.7%] was lost to follow-up) and 71 patients (51.0%) discontinued talquetamab (46 [31.7%] due to PD, 12 [8.3%] due to an AE, 7 [4.8%] due to physician decision, 4 [2.8%] refused treatment, and 1 [0.7%] died).

- **Efficacy and safety update with a clinical cut-off of January 17, 2023**:
  - All Treated Analysis Set: efficacy analysis included 145 patients (Phase 1: 36; Phase 2 Cohort C: 109) who were treated with talquetamab at the RP2D of 0.8 mg/kg Q2W SC.
  - Median duration of follow-up was 12.7 months (range: 0.2 to 26.1 months).
    - Among 104 responders, the median follow-up was 12.7 months (range: 0.2 to 26.1), and 94.2%, 88.5%, and 57.7% of responders had at least 6, 9, and 12 months of follow-up, respectively.
  - The median treatment duration of talquetamab treatment was 8.8 months (range: <0.1 to 25.7).
  - At the clinical cut-off, 41.4% of patients remained on treatment and 58.6% discontinued talquetamab treatment, most frequently due to progressive disease (34.5%).
  - Forty-one patients (28.3%) discontinued study participation (32 [22.1%] died [1 due to COVID-19], 5 [3.4%] withdrew consent, and 1 [0.7%] was lost to follow-up) and 85 patients (58.6%) discontinued talquetamab (50 [34.5%] due to PD, 12 [8.3%] due to an AE, 12 [8.3%] due to physician decision, 6 [4.1%] refused treatment, and 5 [3.4%] died).

B.1.1.2 Response Rates

At the time of the protocol-specified primary analysis (ie, May 16, 2022 cut-off; median follow-up duration: 5.1 months) in the All Treated Analysis Set (n = 145) treated at the RP2D of 0.8 mg/kg Q2W SC, the ORR was 55.2% (95% CI: 46.7, 63.4) as per IRC assessment based on IMWG 2016 criteria (see Table 51 and Figure 17 below) (Janssen 2022e). The primary endpoint was met at the time of primary analysis, and the null hypothesis was rejected as the lower bound of the 95% CI was greater than 30%. Further, 38.6% (95% CI: 30.7, 47.1) of patients had a ≥VGPR, 15.9% (95% CI: 10.3, 22.8) achieved ≥CR, and 9.0% (95% CI: 4.9, 14.8) achieved sCR. In the preplanned sensitivity analysis, the ORRs were 51.7% (95% CI: 43.3%, 60.1%) and 53.8% (95% CI 45.3%, 62.1%) based on a computerized algorithm and investigator assessment, respectively (Janssen 2022e).

At the subsequent efficacy update (i.e., September 12, 2022 cut-off; median follow-up duration: 8.6 months), 26 additional patients responded to talquetamab at the RP2D of 0.8 mg/kg Q2W SC, resulting in a higher ORR than in the primary analysis (73.1% [95% CI: 65.1, 80.1]; see Table 51 and Figure 17) (Janssen 2022d). Notably, the proportion of patients achieving deeper responses to talquetamab increased from the time of primary analysis, including 16 patients (11%) with a new sCR (from 9.0% to 20.0%), 24 patients with a new ≥CR (from 15.9% to 32.4%), and 27 patients with a new ≥VGPR (from 38.6% to 57.2%) (Janssen 2022d).

At the time of the January 17, 2023 clinical cut-off, 2 patients (1.4%) were reclassified as having stable disease, and the ORR decreased from 73.1% at the time of the September 12, 2022 clinical cut-off to 71.1% (95% CI: 63.7, 78.9) (Janssen 2023e).

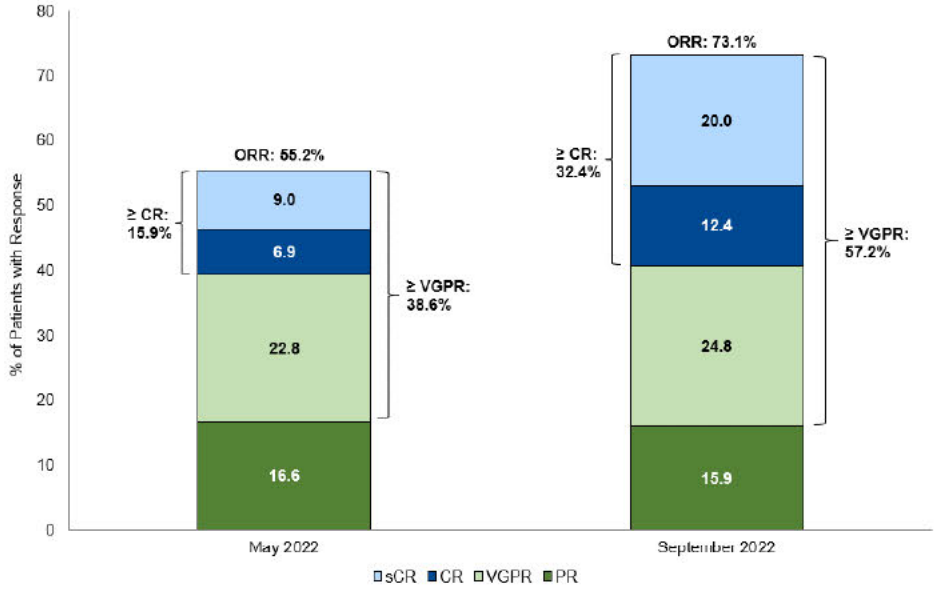
Table 51. Overall best confirmed response rates for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (May 16, 2022; September 12, 2022; and January 17, 2023 cut-offs)

Outcome	May 16, 2022 Primary Analysis All Treated Analysis Set	September 12, 2022 Efficacy Update All Treated Analysis Set	January 17, 2023 Efficacy Update All Treated Analysis Set
Response Rates[a], n (%; 95% CI)	**n = 145**	**n = 145**	**n = 145**
ORR (sCR + CR + VGPR + PR)	80 (55.2%; 46.7, 63.4)	106 (73.1%; 65.1, 80.1)	104 (71.7%; 63.7, 78.9)

Outcome	May 16, 2022 Primary Analysis All Treated Analysis Set	September 12, 2022 Efficacy Update All Treated Analysis Set	January 17, 2023 Efficacy Update All Treated Analysis Set
VGPR or better (sCR + CR + VGFR)	56 (38.6%; 30.7, 47.1)	83 (57.2%; 48.8, 65.4)	88 (60.7%; 52.2, 68.7)
CR or better (sCR + CR)	23 (15.9%; 10.3, 22.8)	47 (32.4%; 24.9, 40.7)	56 (38.7%; 30.7, 47.1)
sCR	13 (9.0%; 4.9, 14.8)	29 (20.0%; 13.8, 27.4)	43 (29.7%; 22.4, 37.8)
CR	10 (6.9%; 3.4, 12.3)	18 (12.4%; 7.5, 18.9)	13 (9.0%; 4.9, 14.8)
VGPR	33 (22.8%; 16.2, 30.5)	36 (24.8%; 18.0, 32.7)	32 (22.1%; 15.6, 29.7)
PR	24 (16.6%; 10.9, 23.6)	23 (15.9%; 10.3, 22.8)	16 (11.0%; 6.4, 17.3)
MR	4 (2.8%; 0.8, 6.9)	0 (NE, NE)	0 (NE, NE)
SD	45 (31.0%; 23.6, 39.2)	25 (17.2%; 11.5, 24.4)	27 (18.6%; 12.6, 25.9)
PD	9 (6.2%; 2.9, 11.5)	9 (6.2%; 2.9, 11.5)	9 (6.2%; 2.9, 11.5)
Not evaluable	7 (4.8%; 2.0, 9.7)	5 (3.4%; 1.1, 7.9)	5 (3.4%; 1.1, 7.9)

[a] Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: Percentages were calculated with the number of patients in the All Treated Analysis Set as the denominator; exact 95% CIs are provided.
Abbreviations: CI = confidence interval; CR = complete response rate; IMWG = International Myeloma Working Group; IRC = independent review committee; MR = minimal response; NE = not estimable; ORR = overall response rate; PD = progressive disease; PR = partial response; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.
Sources: (Janssen 2022e, Janssen 2022c, Janssen 2023e).

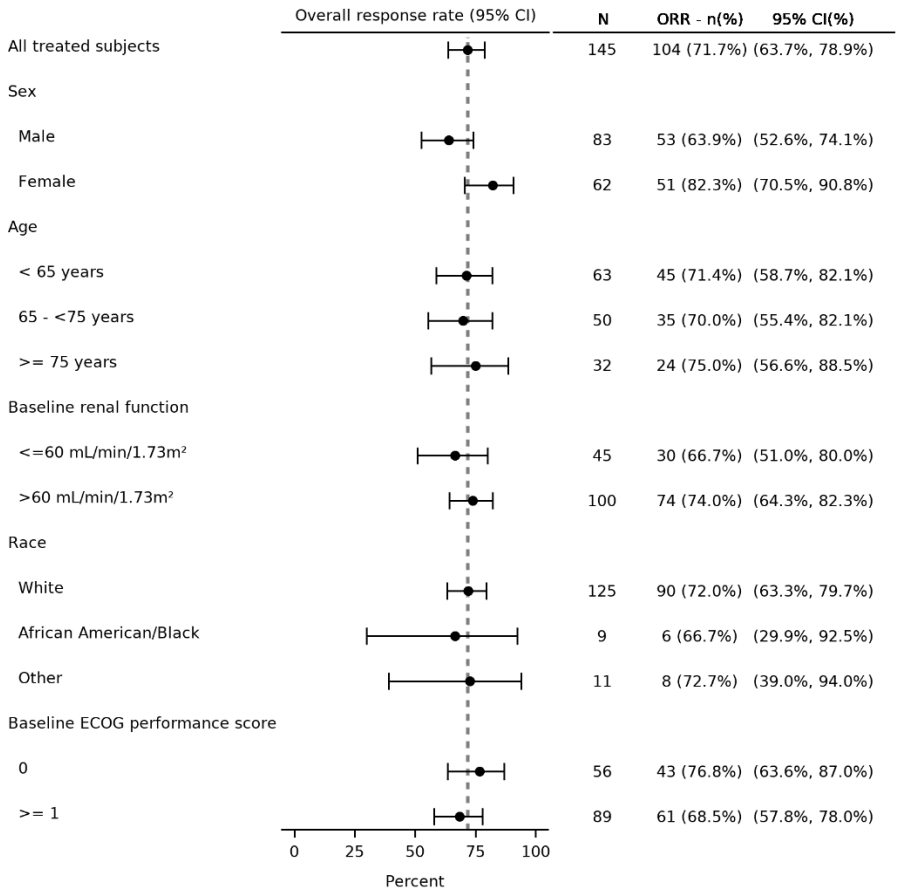
Figure 17. Overall best response to talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (May 16, 2022 and September 12, 2022 cut-offs)



Abbreviations: CR = complete response; ORR = overall response rate; Q2W = every two weeks; PR = partial response; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; sCR = stringent complete response; VGPR = very good partial response.
Source: (Janssen 2022e, Janssen 2022c, Janssen 2023e).

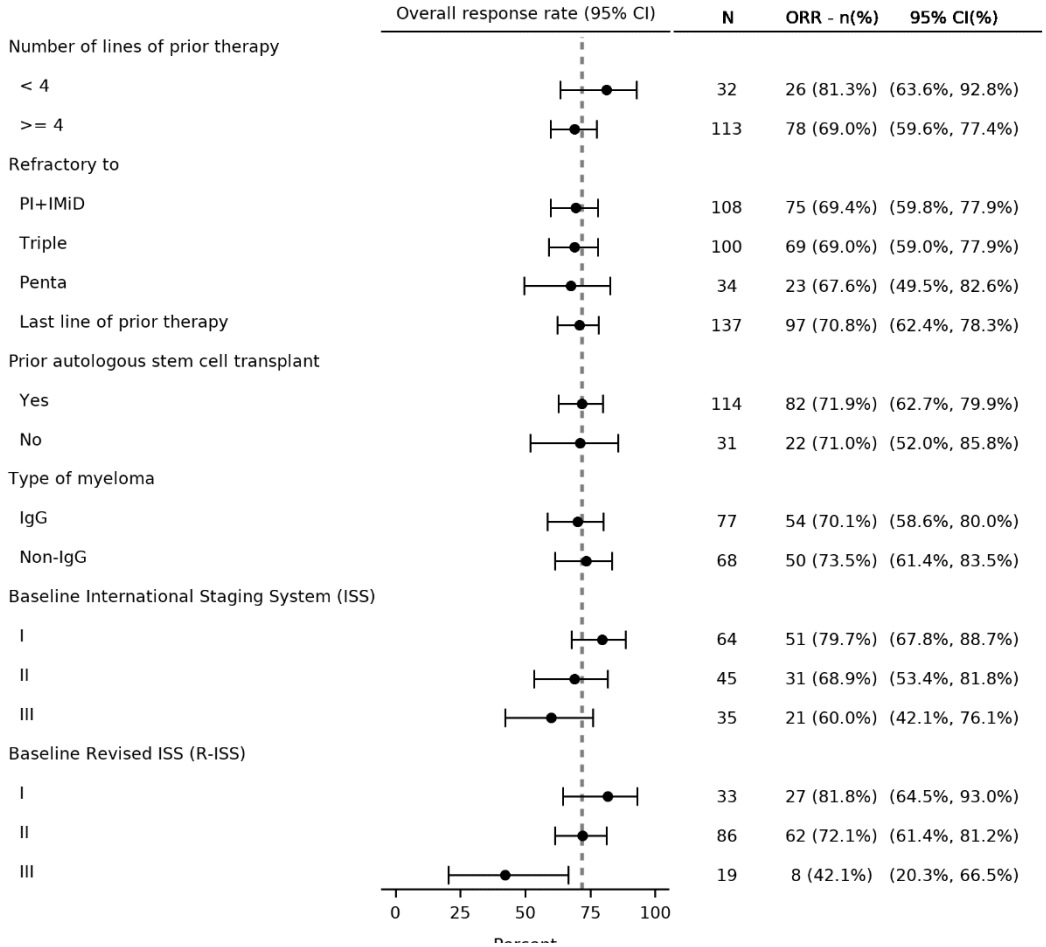
Subgroup analyses demonstrated that the ORR was generally consistent across most clinically relevant subgroups, including demographic and clinical characteristics, number of prior LOTs, refractoriness to prior therapy, cytogenetic risk at baseline, and baseline GPRC5D expression (Janssen 2023e). The forest plot of ORR subgroup analyses from the January 17, 2023 clinical cut-off are presented below in Figure 18, Figure 19, and Figure 20. Response rates were lower in patients with extramedullary plasmacytomas at baseline. However, it should be noted that interpretations of ORR were limited in some subgroups by small sample sizes.

Figure 18. Forest plot of ORR subgroup analyses for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off; Panel A)



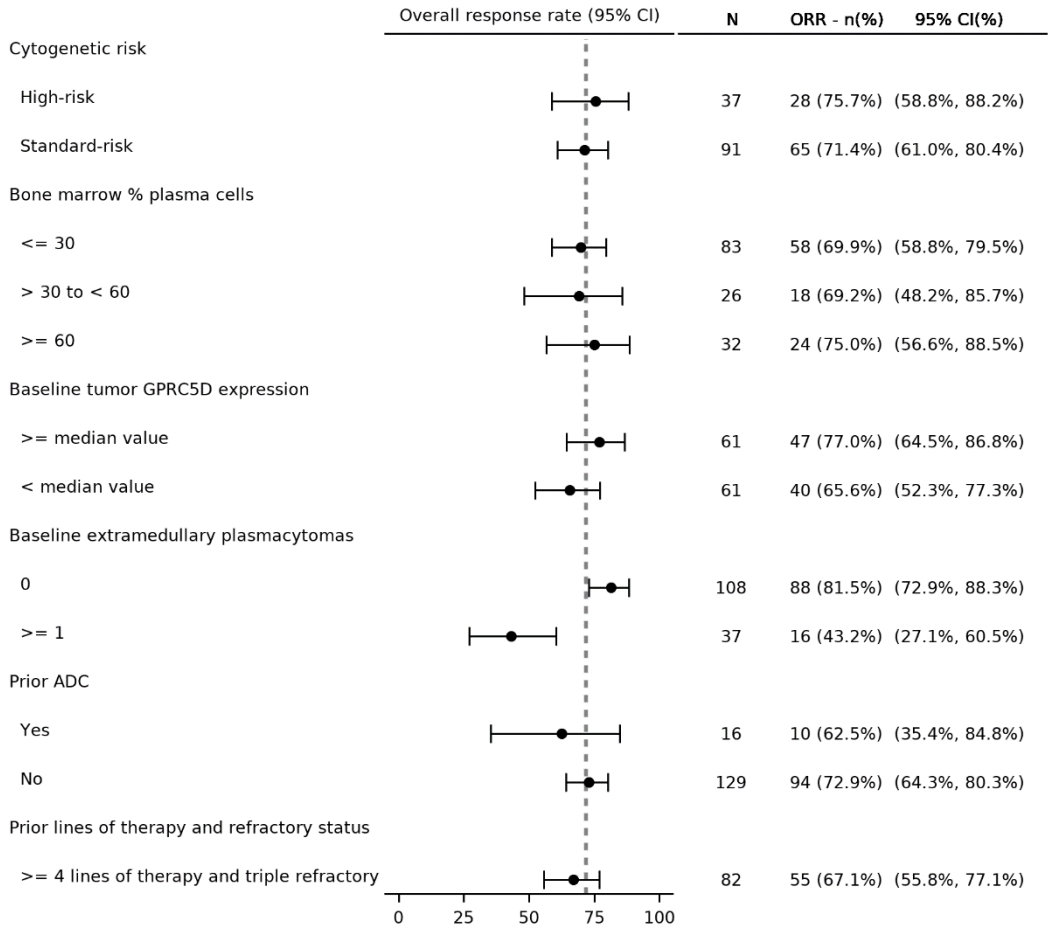
Note: For race, other includes Asian (6 patients), Multiple (1 patients), Native Hawaiian or Other Pacific Islander (1 patients), Unknown (1 patients) and Not Reported (2 patients).
Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Source: (Janssen 2023e).

Figure 19. Forest plot of ORR subgroup analyses for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2022 cut-off; Panel B)



Note: Refractory includes last line of prior therapy, PI + IMiD, Triple (PI + IMiD + anti-CD38 mAb), Penta (≥2 PIs + ≥2 IMiDs + 1 anti-CD38 mAb).
Note: Baseline ISS was based on the combination of serum β2-microglobulin and albumin. Baseline R-ISS was based on the combination of serum β2-microglobulin and albumin, genetic risk, and the level of LDH.
Abbreviations: CI = confidence interval; IgG = immunoglobulin G; IMiD = immunomodulatory drug; ISS = International Staging System; LDH = lactate dehydrogenase; mAb = monoclonal antibody; ORR = overall response rate; PI = proteasome inhibitor; Q2W = every two weeks; RP2D = recommended Phase 2 dose; R-ISS = Revised ISS; SC = subcutaneous.
Source: (Janssen 2023e).

Figure 20. Forest plot of ORR subgroup analyses for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off; Panel C)



Note: High-risk is defined as having t(4; 14); t(14; 16) and/or 17p deletion.
Abbreviations: ADC = antibody-drug conjugate; CI = confidence interval; GPRC5D = G-protein coupled receptor family C group 5 member D; ORR = overall response rate; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Source: (Janssen 2023e).

B.1.1.3 Duration of Response

At the time of the May 16, 2022 clinical cut-off (median follow-up: 6.0 months for responders; Phase 1 and Phase 2 Cohort C), DOR data were immature, with 81.3% of responders censored (see Table 52) (Janssen 2022e). The proportion of responders who maintained a response for at least 6 and 9 months was estimated at 78.5% (95% CI: 63.9, 87.7) and 72.9% (95% CI: 54.3, 84.9), respectively. The estimated 6-month DOR was 90.2% (95% CI: 65.9 to 97.5) among the 23 patients who achieved ≥CR, 75.9% (95% CI: 44.1, 91.1) for the 33 patients who achieved VGPR as the best response, and 63.1% (95% CI: 34.6, 81.9) among the 24 patients who achieved PR as the best response (Janssen 2022e). In sensitivity analyses, the DOR based on IRC assessment was comparable with that of a computerized algorithm and investigator assessment; refer to the CSR for additional details (Janssen 2022e).

At the time of the September 12, 2022 clinical cut-off (median follow-up for all responders: 8.8 months), DOR data remained immature, with 77.4% of responders censored (see Table 52 and Figure 21 below) (Janssen 2022d). The proportion of patients estimated to be in response at 6 and 9 months was 80.7% and 72.6%, respectively. Additionally, the DOR among patients with at least 4 prior LOTs was comparable with the overall population treated at the RP2D of 0.8 mg/kg

Q2W SC (6-month DOR: 85.7% [95% CI: 74.7, 92.1]; 9-month DOR: 73.3% [95% CI: 52.4, 86.1] (Janssen 2022d). Patients with deeper responses to talquetamab also had more durable responses (6-month DoR; ≥CR: 95.6% [95% CI 83.4, 98.9]; ≥VGPR: 80.3% [95% CI: 61.0, 90.7]; PR: 37.9% [95% CI: 12.1, 64.1]). Among patients who achieved ≥CR, the mDoR was not estimable, whereas patients who achieved ≥VGPR or PR had a mDOR of 8.7 months (95% CI: 7.0, NE) or 5.5 months (95% CI: 1.9, NE), respectively.

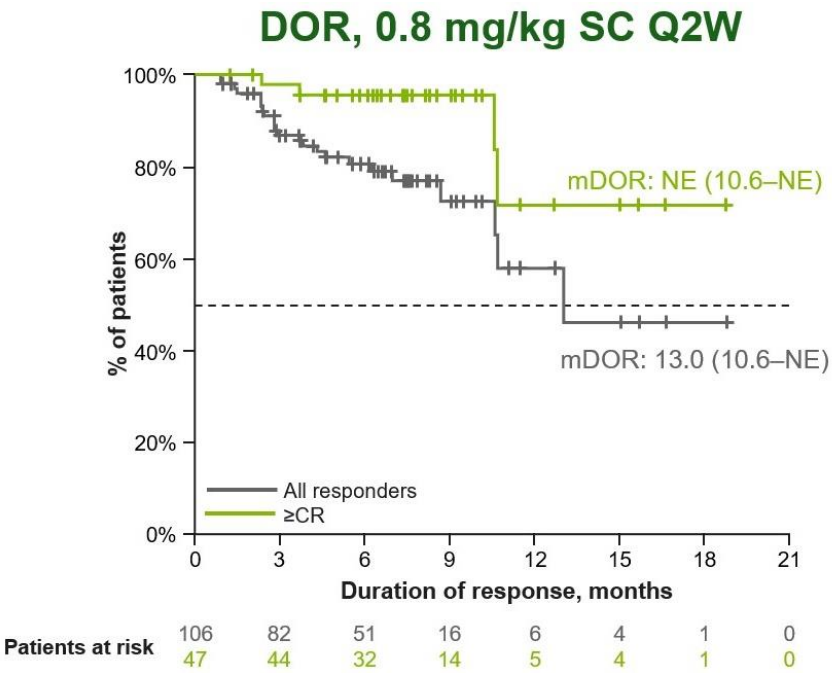
At the time of the January 17, 2023 clinical cut-off (median follow-up for all responders: 12.9 months), the mDOR was not yet reached (95% CI: 13.0, NE; see Table 52 below), with data censored for 73.1% of responders (Janssen 2023e). The probability of responders remaining in response at 6 and 9 months were consistent with those observed in previous clinical cut-offs at 82.2% (95% CI: 73.2, 88.4) and 76.3% (95% CI: 66.5, 83.7), respectively, and 69.3% (95% CI: 57.8, 78.2) were estimated to maintain a response at 12 months. Further, responses continued to be even more durable among patients with deeper responses. The estimated 6-month DOR was 96.4% (95% CI: 86.5, 99.1) among 56 patients who achieved ≥CR, 79.8% (95% CI: 60.4, 90.4) among 32 patients who achieved VGPR as the best response, and 30.0% (95% CI: 8.9, 54.9) among 16 patients who achieved PR as the best response. The 12-month DOR rate was 78.9% among patients with ≥CR (Schinke et al. 2023). Individual patient responses to talquetamab 0.8 mg/kg Q2W SC are shown below in Figure 22; most responses occurred rapidly (ie, by the start of Cycle 2) and deepened over time (Janssen 2022e, Janssen 2022c, Janssen 2023e).

Table 52. DOR among responders in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; 0.8mg/kg Q2W SC), All Treated Analysis Set (May 16, 2022; September 12, 2022; and January 17, 2023 cut-offs)

Outcome	May 16, 2022 Primary Analysis All Treated Analysis Set	September 12, 2022 Efficacy Update All Treated Analysis Set	January 17, 2023 Efficacy Update All Treated Analysis Set
DOR in Responders[a]	**n = 80**	**n = 106**	**n = 104**
Number of events, n (%)	15 (18.8%)	24 (22.6%)	28 (26.9%)
Number of censored, n (%)	65 (81.3%)	82 (77.4%)	76 (73.1%)
Median Kaplan–Meier DOR estimate, mo 25% percentile (95% CI) Median (95% CI) 75% percentile (95% CI) Range	 6.2 (3.7, 13.0) 13.0 (10.6, NE) NE (13.0, NE) (0+, 15+)	 8.7 (4.3, 13.0) 13.0 (10.6, NE) NE (13.0, NE) (0+, 19+)	 9.3 (4.6, NE) NE (13.0, NE) NE (NE, NE) (0+, 22+)
6-month event-free rate, % (95% CI)	78.5% (63.9, 87.7)	80.7% (71.0, 87.4)	82.2 (73.2, 88.4)
9-month event-free rate, % (95% CI)	72.9% (54.3, 84.9)	72.6% (58.2, 82.7)	76.3 (66.5, 83.7)
12-month event-free rate, % (95% CI)	N/A	N/A	69.3% (57.8, 78.2)

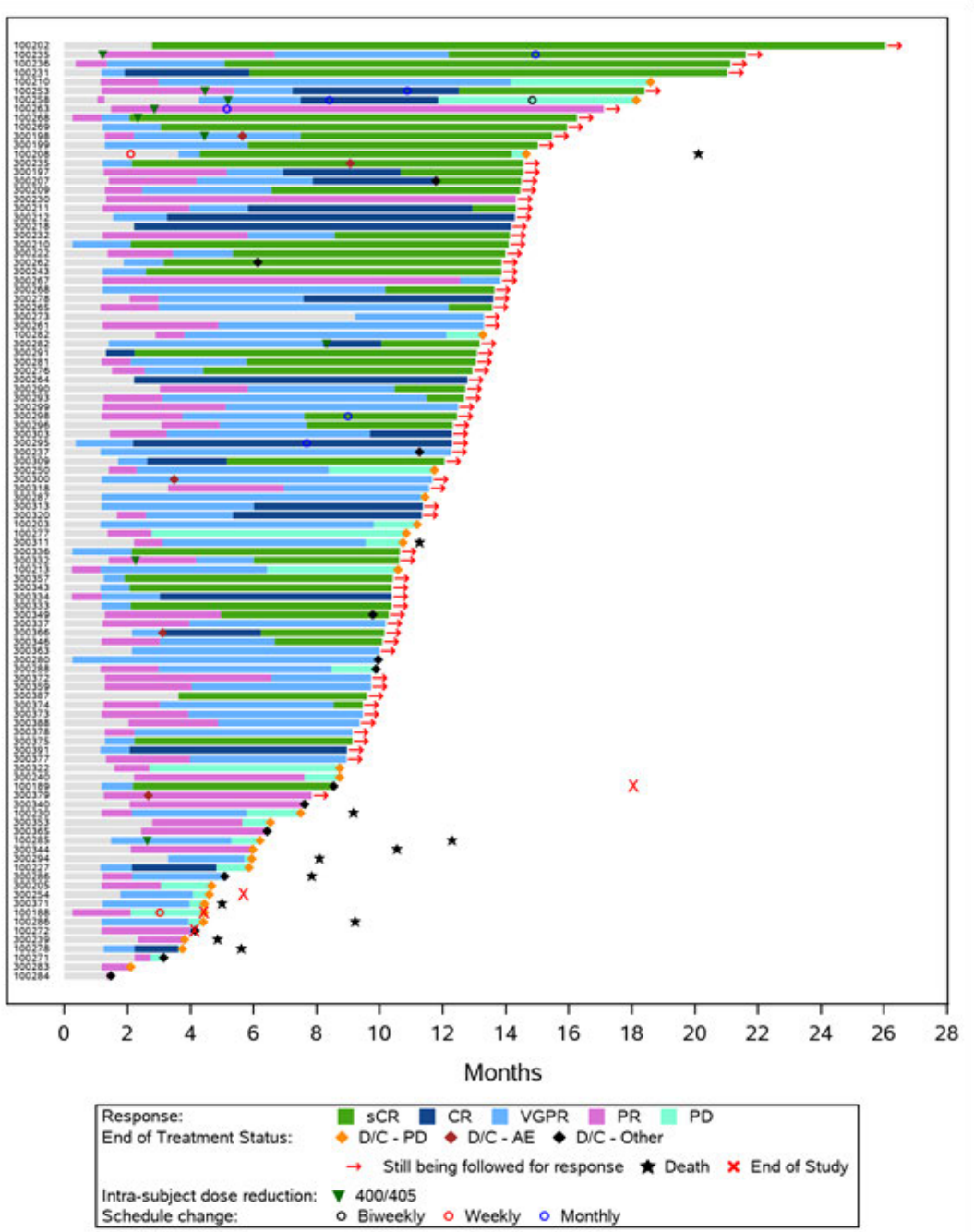
[a] DOR was calculated as the number of months from first documented response to progression or death due to any cause.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to any cause.
Note: Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
Abbreviations: CI = confidence interval; DOR = duration of response; IRC = independent review committee; IMWG = international myeloma working group; mo = months; N/A = not available; NE = not estimable; + = censored observation; PR = partial response; Q2W = every two weeks; RP2D = recommended Phase 2 dose.
Source: (Janssen 2022e, Janssen 2022c, Janssen 2023e).

Figure 21. Kaplan–Meier plot for DOR to talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C) as stratified by response status (≥CR vs. all responders), RP2D 0.8 mg/kg Q2W SC, All Treated Analysis Set (September 12, 2022 cut-off)



Note: Response was assessed by IRC, based on IMWG consensus criteria (2016). Median follow-up: 8.6 months (range: 0.2-22.5).
Abbreviations: CR = complete response; DOR = duration of response; IMWG = International Myeloma Working Group; IRC = independent review committee; NE = not evaluable; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Source: (Janssen 2022d).

Figure 22. Responses over time among patients who had an overall response in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)



Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).
Note: With sponsor approval, participants in part 3 were allowed to change dosing schedule of talquetamab from 0.4 mg/kg Q1W SC to 0.8 mg/kg Q2W SC if they had achieved a response of CR or better for at least 6 months
Abbreviations: CR = complete response; D/C = discontinued; IMWG = international myeloma working group; IRC = independent review committee; PD = progressive disease; PR = partial response; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; sCR = stringent response; VGPR = very good partial response.
Source: (Janssen 2023e).

B.1.1.4 Survival Outcomes

At a median follow-up of 5.1 months (May 16, 2022 clinical cut-off), data for PFS was immature for patients treated at the RP2D of 0.8 mg/kg Q2W SC, with an estimated 6-month PFS rate of 58.5% (95% CI: 47.1, 68.3; see Table 53) (Janssen 2022e). Of the 100 patients (69.0%) who were censored from the PFS analysis, 92 (92.0%) had not progressed or died, 6 (6.0%) started subsequent antimyeloma therapy before disease progression or death, and 2 (2.0%) withdrew consent. Of the 45 reported PFS events, 38 (84.4%) were due to PD, and 7 (15.6%) of patients died without PD. Refer to CSR for results of the preplanned sensitivity analyses for PFS (Janssen 2022e). At the September 12, 2022 cut-off (median follow-up: 8.6 months), the PFS results remained immature, with PFS data censored for 88 patients (60.7%; see Table 53) (Janssen 2022d). The estimated 6-month and 9-month PFS rates were 64.8% (95% CI: 56.1, 72.3) and 59.1% (95% CI: 49.7, 67.3), respectively, similar to the primary analysis.

With an additional four-months of follow-up (January 17, 2023 cut-off; median follow-up: 12.7 months), the mPFS was 14.2 months (95% CI: 9.6, NE) among patients treated with talquetamab 0.8 mg/kg Q2W SC (Janssen 2023e). However, these results are not yet mature as PFS data was censored for 81 patients (55.9%). Most of the censored patients (69 [85.2%]) had not progressed or died at the January 17, 2023 cut-off, 10 patients (12.3%) started subsequent antimyeloma therapy before disease progression or death, and 2 patients (2.5%) withdrew consent. Of the 64 reported PFS events, 56 events (87.5%) were progressive disease, and 8 events (12.5%) were death without progressive disease. At both 9 and 12 months, more than half of patients in the 0.8 mg/kg Q2W SC cohort were estimated to remain free from disease progression (9 months: 58.9% [95% CI: 50.2, 66.6]; 12 months: 54.4% [95% CI: 45.3, 62.6]; see Table 53 and Figure 5) (Janssen 2023e, Schinke et al. 2023).

Table 53. PFS results for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8mg/kg Q2W SC), All Treated Analysis Set (May 16, 2022, September 12, 2022, and January 17, 2023 cut-offs)

PFS Results	May 16, 2022 Primary Analysis All Treated Analysis Set (n = 145)	September 12, 2022 Efficacy Update All Treated Analysis Set (n =145)	January 17, 2023 Efficacy Update All Treated Analysis Set (n = 145)
Number of events, n (%)	45 (31.0%)	57 (39.3%)	64 (44.1%)
Number of events censored, n (%)	100 (69.0%)	88 (60.7%)	81 (55.9%)
Median Kaplan–Meier estimate, mo 25% percentile (95% CI) Median (95% CI) 75% percentile (95% CI)	 3.0 (2.1, 4.8) 14.2 (5.4, NE) 14.2 (14.2, NE)	 3.6 (2.5, 5.3) 11.9 (8.4, NE) NE (14.2, NE)	 3.6 (2.5, 5.3) 14.2 (9.6, NE) NE (NE, NE)
6-month PFS rate, % (95% CI)	58.5% (47.1, 68.3)	64.8% (56.1, 72.3)	63.5 (54.9, 70.9)
9-month PFS rate, % (95% CI)	55.3% (42.7, 66.2)	59.1% (49.7, 67.3)	58.9% (50.2, 66.6)
12-month PFS rate, % (95% CI)	-	-	54.4% (45.3, 62.6)

Note: PD was assessed by the IRC, based on IMWG consensus criteria (2016).
Abbreviations: CI = confidence interval; IMWG = International Myeloma Working Group; mo = months; NE = Not estimable; PD = progressive disease; PFS = progression-free survival; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Sources: (Janssen 2022e, Janssen 2022c, Janssen 2023e, Schinke et al. 2023).

At the time of the May 16, 2022 clinical cut-off, a total of 18 (12.4%) deaths were observed among patients who received treatment with talquetamab at the RP2D of 0.8 mg/kg Q2W (see Table 54.) (Janssen 2022g). The mOS has not been reached, and the 6-month and 9-month OS rates were 84.7% (95% CI: 75.5, 90.6) and 80.0% (95% CI: 65.6, 88.8), respectively. At the subsequent efficacy update (ie, September 12, 2022 cut-off; median follow-up duration: 8.6 months), the results for OS continued to be immature; OS data was censored for 118 patients (81.4%; see Table 54.) (Janssen 2022d). The Kaplan-Meier estimated OS rates at 6 and 9 months were comparable with that of the primary analysis, at 85.7% (95% CI: 78.6, 90.5) and 82.4% (95% CI: 74.4, 88.0), respectively. Overall, patients treated with talquetamab 0.8 mg/kg Q2W SC demonstrated high rates of OS after a median follow-up duration of 8.6 months, suggesting that talquetamab provides a substantial survival benefit to patients with heavily pretreated RRMM.

With an additional four months of follow-up (January 17, 2023 clinical cut-off; median follow-up: 12.7 months), OS data was censored for 112 patients (77.2%) in the 0.8 mg/kg Q2W SC cohort and the OS results were not mature (see Table 54. and Figure 6) (Janssen 2023e). The estimated OS rates at 6-, 9-, and 12-months were consistent with prior clinical cut-offs at 85.2% (95% CI: 78.2, 90.1), 83.0% (95% CI: 75.8, 88.3), and 77.4% (95% CI: 69.1, 83.7), respectively (Janssen 2023e, Schinke et al. 2023).

Table 54. OS results for talquetamab in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8mg/kg Q2W SC), All Treated Analysis Set (May 16, 2022, September 12, 2022, and January 17, 2023 cut-offs)

OS Results	May 16, 2022 Primary Analysis All Treated Analysis Set (n = 145)	September 12, 2022 Efficacy Update All Treated Analysis Set (n = 145)	January 17, 2023 Efficacy Update All Treated Analysis Set (n = 145)
Number of events, n (%)	18 (12.4%)	27 (18.6%)	33 (22.8%)
Number of events censored, n (%)	127 (87.6%)	118 (81.4%)	112 (77.2%)
Median Kaplan–Meier estimate, mo 25% percentile (95% CI) Median (95% CI) 75% percentile (95% CI)	 9.2 (8.1, NE) NE (NE, NE) NE (NE, NE)	 15.0 (8.1, NE) 20.1 (20.1, NE) NE (20.1, NE)	 15.0 (9.2, NE) NE (20.1, NE) NE (NE, NE)
6-month OS rate, % (95% CI)	84.7% (75.5, 90.6)	85.7% (78.6, 90.5)	85.2% (78.2, 90.1)
9-month OS rate, % (95% CI)	80.0% (65.6, 88.8)	82.4% (74.4, 88.0)	83.0% (75.8, 88.3)
12-month OS rate, % (95% CI)	-	-	77.4% (69.1, 83.7)

Abbreviations: CI = confidence interval; mo = months; NE = not estimable; OS = overall survival; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous.
Sources: (Janssen 2022e, Janssen 2022c, Janssen 2023e, Schinke et al. 2023).

B.1.1.5 Time to Next Treatment

At the time of the May 16, 2022 clinical cut-off clinical cut-off, 37 patients (25.5%) had initiated subsequent anti-myeloma therapy and/or died due to PD, with a mTTNT of 11.2 months (95% CI: 7.7, NE) (Janssen 2022e). The therapy most frequently administered (≥5% of patients) after talquetamab was cyclophosphamide (5.5%); 2.8% of patients received CAR-T therapy. At the time of the September 12, 2022 clinical cut-off, an additional 11 patients initiated subsequent anti-myeloma therapy and/or died due to PD (overall: 48 patients [33.1%]), with an estimated 6-month rate of 74.0% (95% CI: 65.7, 80.6) (Janssen 2022b, Janssen 2022d). With an additional 4-months of follow-up (January 17, 2023 clinical cut-off), subsequent anti-myeloma therapy and/or death due to PD was reported for 65 patients (44.8%) in the 0.8 mg/kg Q2W SC cohort, with a mTTNT of 16.3 months (95% CI: 11.2, 18.6) (Janssen 2023e, Janssen 2023g).

B.2 Results per study – MajesTEC-1

Table 55. Results per MajesTEC-1 (NCT03145181, NCT04557098)

Results of MajesTEC-1 (NCT03145181, NCT04557098)											
				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		
ORR, %	Phase 1 & Phase 2 Cohort A (pooled)	165	63.0% (55.2, 70.4)	N/A	N/A	N/A	N/A	N/A	N/A	ORR was defined as the proportion of participants who achieved a PR or better according to the IMWG criteria on the chosen index line therapy, adjudicated by an IRC	(Janssen 2023e)
CR or better, %	Phase 1 & Phase 2 Cohort A (pooled)	165	45.5% (37.7, 53.4)	N/A	N/A	N/A	N/A	N/A	N/A	CR or better rate was defined as the percentage of participants achieving CR or sCR according to IMWG criteria, adjudicated by an IRC	(Janssen 2023e)
VGPR or better, %	Phase 1 & Phase 2 Cohort A (pooled)	165	59.4% (51.5, 67.0)	N/A	N/A	N/A	N/A	N/A	N/A	VGPR or better rate was defined as the percentage of participants achieving VGPR or better according to IMWG criteria, adjudicated by an IRC	(Janssen 2023e)

Results of MajesTEC-1 (NCT03145181, NCT04557098)											
				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		
DOR, months (median)	Phase 1 & Phase 2 Cohort A (pooled)	104	21.6 (16.2, NE)	N/A	N/A	N/A	N/A	N/A	N/A	DOR was calculated among responders (with a PR or better response) from the date of initial documentation of a response to the date of first documented evidence of progressive disease as defined in the IMWG criteria, or death due to any cause	(Janssen 2023e)
PFS, median (months)	Phase 1 & Phase 2 Cohort A (pooled)	165	11.3 (8.8, 16.4)	N/A	N/A	N/A	N/A	N/A	N/A	PFS was evaluated according to IMWG criteria, adjudicated by an IRC	(Janssen 2023e)
TTNT, months (median)	Phase 1 & Phase 2 Cohort A (pooled)	165	20.1 (12.7, NE)	N/A	N/A	N/A	N/A	N/A	N/A	Subsequent anti-myeloma therapy was reported for 78 subjects (47.3%)	(Janssen 2023e)
OS, median (months)	Phase 1 & Phase 2 Cohort A (pooled)	165	21.9 (15.1, NE)	N/A	N/A	N/A	N/A	N/A	N/A	Participants who had not progressed and were alive at the data cut-off, were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy. Participants still alive or the vital status was	(Janssen 2023e)

Results of MajesTEC-1 (NCT03145181, NCT04557098)												
				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		
										unknown were censored at the date last known to be alive	

Abbreviations: CI, Confidence Interval; CR, Complete Response; DOR, Duration of Response; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; NE, not evaluable; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-free Survival; Q1W, weekly; Q2W, every two weeks; sCR, Stringent Complete Response; TTNT, Time to Next Treatment; VGPR, Very Good Partial Response

Appendix C. Comparative analysis of efficacy

C.1 Methodology of adjusted comparison of talquetamab versus real-world physician's choice

C.1.1 Identification of prognostic factors for balancing

Methodologic guidance on prognostic variable selection for confounding control emphasizes the importance of subject matter expertise in identifying the most important prognostic factors with the greatest potential to result in biased treatment effect estimates (VanderWeele 2019). Baseline factors were identified a priori by clinical experts as important prognostic factors in the setting of later-line relapsed or refractory multiple myeloma.

The list of factors and their availability in MonumenTAL-1 and MajesTEC-1 is shown in Table 56, all 17 factors were available in both trials.

Table 56. Availability of prognostic factors in MonumenTAL-1 and MajesTEC-1

Prognostic factor	Available in MonumenTAL-1?	Available in MajesTEC-1?	Categories
Refractory status	Yes	Yes	Penta refractory: refractory to ≥2 IMiDs, ≥2 Pis, and 1 anti-CD38 monoclonal antibody Quad refractory: refractory to ≥2 ImiDs, 1 PI, and 1 anti-CD38 monoclonal antibody or ≥2 Pis, 1 ImiD, and 1 anti-CD38 monoclonal antibody Triple refractory: refractory to 1 ImiD, 1 PI, and 1 anti-CD38 monoclonal antibody ≤ Double refractory: refractory status of less than triple refractory
ISS stage	Yes	Yes	I II III
Time to progression on last regimen	Yes	Yes	< 3 months ≥ 3 months
Extramedullary plasmacytoma[2]	Yes	Yes	Yes No

Number of prior lines of therapy	Yes	Yes	≤ 4 > 4
Years since multiple myeloma diagnosis	Yes	Yes	< 6 ≥ 6
Average duration of prior lines (months)	Yes	Yes	< 10 10-14 ≥ 15
Age	Yes	Yes	< 65 ≥ 65
Hemoglobin (g/dL)	Yes	Yes	< 12 ≥ 12
LDH levels (units/L)	Yes	Yes	< 280 ≥ 280
Creatinine clearance	Yes	Yes	<60 60 to <90 ≥ 90
ECOG status	Yes	Yes	0 1-2
Sex	Yes	Yes	Male Female
Type of multiple myeloma	Yes	Yes	IgG Non-IgG
Prior stem cell transplant	Yes	Yes	Yes No
Race	Yes	Yes	White Other/Not reported
Cytogenetic profile	Yes	Yes	High risk: at least 1 of del17p, t(4;14), or t(14;16) Standard risk: any other abnormality Missing

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ImiD, immunomodulatory imide drug; ISS, International Staging System; LDH, lactate dehydrogenase; PI, proteasome inhibitor;
[2] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas.(Caers et al. 2018)

C.1.2 Handling missing data in selected prognostic factors

For the MonumenTAL-1 0.8 mg/kg Q2W SC cohort, low risk imputation was used to impute missingness for ISS stage (0.7% missing). For MajesTEC-1, low risk imputation was used to impute missingness for several variables

(proportion of missing data in parentheses): ISS stage (1.8%), years since multiple myeloma diagnosis (0.6%), time to progression on last regimen (1.2%), and average duration of prior lines (0.6%). Data for cytogenetic profile were missing in 10.3% of participants from the MajesTEC-1 cohort, and 11.7% of participants from the talquetamab 0.8 mg/kg Q2W cohort; however, imputation was not done for cytogenetic profile and instead, 'missing' was added as a categorical variable.

C.1.3 Balance of populations

The analyses weighted participants on the following factors: refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines of therapy, age, hemoglobin levels, LDH levels, creatinine clearance, ECOG status, sex, type of multiple myeloma, prior stem cell transplant, race, and cytogenetic profile.

Error! Reference source not found. and Table 11 provide the participant numbers for both MonumenTAL-1 and MajesTEC-1 for all baseline risk factors by categories, including SMD values as measure of balance, with SMD ≤0.20 indicating balance between both cohorts. Before reweighting, the talquetamab 0.8 mg/kg Q2W SC cohort had a higher proportion of participants who were double refractory (31.0% vs 22.4%), with ISS stage III disease (24.1% vs 12.1%), and with extramedullary plasmacytomas (25.5% vs 17.0%). In contrast to the talquetamab 0.8 mg/kg Q2W SC cohort, MajesTEC-1 had a greater proportion of participants who were quad-refractory (35.2% vs 28.3%), penta-refractory (30.3% vs 24.1%), and with ISS stage I disease (52.7% vs 44.8%).

In the primary ATC analyses, the reweighted MonumenTAL-1 cohorts were well balanced with the MajesTEC-1 cohort on all baseline characteristics, with all SMDs below 0.11 for the 0.8 mg/kg Q2W SC cohort. Considering all factors, the number of variables with SMD>0.2 reduced from 3 prior to weighting to none after weighting in comparisons with the 0.8 mg/kg Q2W cohort. In the ATT sensitivity analyses, the reweighted MajesTEC-1 cohort was also well balanced with the 0.8 mg/kg Q2W SC cohort on all baseline characteristics, with all SMDs below 0.10.

A visual presentation of the SMDs before weighting (unadjusted) and after weighting (adjusted) from Error! Reference source not found. and Table 11 is provided in Figure 23. The overall distributional balance of the prognostic variables before and after weighting are shown in Figure 24.

Figure 23. Balance of Prognostic Variables Before and After Weighting for the (A) Main ATC Analysis and (B) Sensitivity ATT Analysis – All Treated Analysis Set

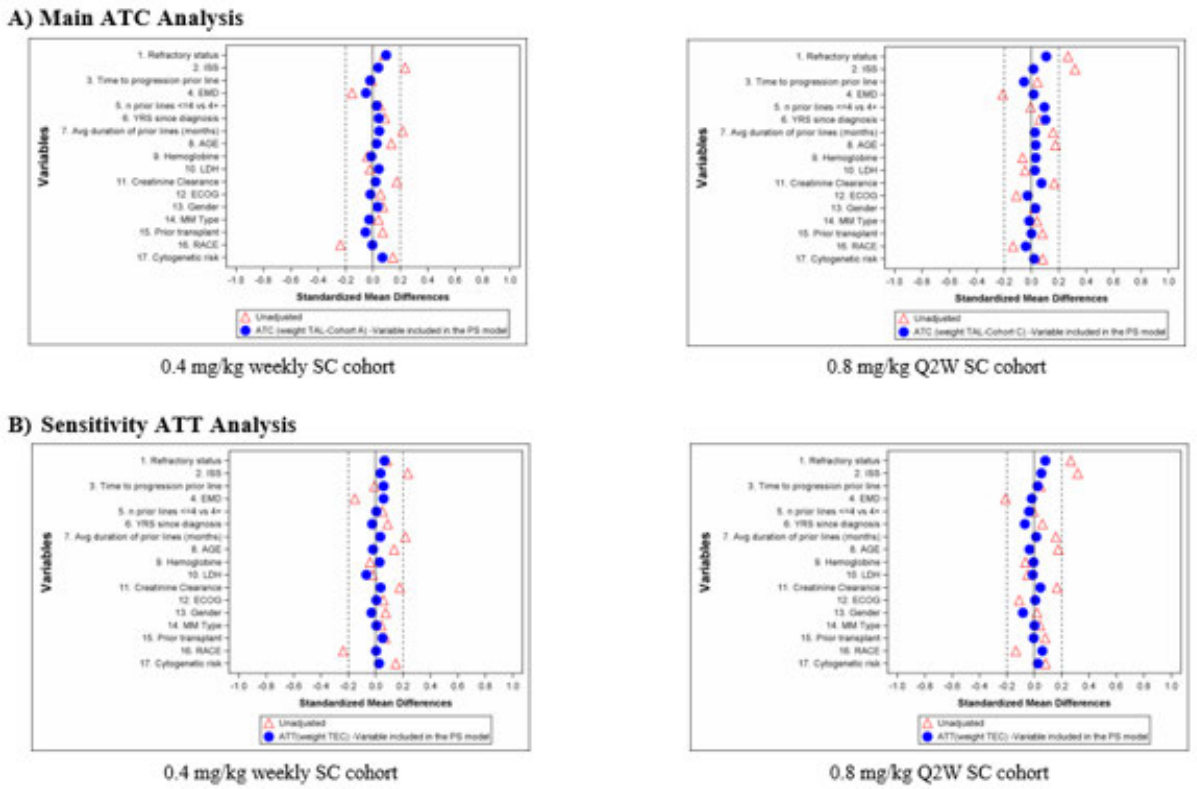
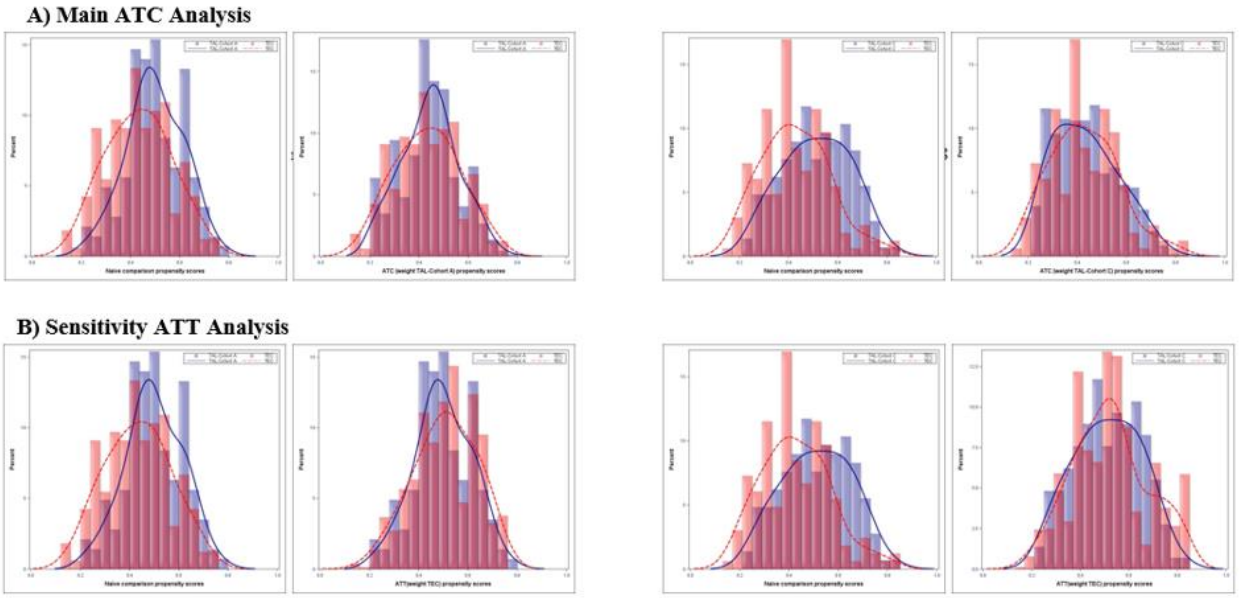


Figure 24 Distributional Balance for the Unadjusted and Adjusted (A) Main ATC Analysis (B) Sensitivity ATT Analysis – All Treated Analysis Set



C.1.4 Statistical method

IPTW with ATC weighting was chosen for the main analyses. Propensity scores for MonumenTAL-1 were first estimated using multivariable logistic regression (including baseline characteristics as prognostic variables), which were subsequently converted to weights. The weights for participants in MajesTEC-1 were, (ATCw)̃_1k=1 (k=1,2,⋯,n_1), and the weights for participants in MonumenTAL-1 were, p̃_0k, were (ATCw)̃_0k= 〖1-p̃〗_0k/p̃_0k (k=1,2,⋯,n_0), where n_1 and n_0 were the sample sizes for MajesTEC-1 and MonumenTAL-1, respectively. Weighted logistic and proportional hazards regressions were used to estimate relative treatment effects in the MonumenTAL-1 and MajesTEC-1 populations for binary and time-to-event endpoints, respectively. This propensity-score based method allowed the MonumenTAL-1 population to be aligned with the MajesTEC-1 population. IPTW was possible given the overlap in the propensity score distribution between the cohorts, and is an efficient method when the sample size is small relative to the number of potential baseline confounding factors (Li et al. 2018). Weightings were scaled such that they improved balance of prognostic variables and summed to the original number of participants in MajesTEC-1. ATT weights were utilized as sensitivity analyses.

Multivariable regression was also conducted as a sensitivity analysis. Similar to IPTW, this method also requires sufficient overlap in the prognostic variable distributions between the cohorts; however, relative treatment effects were estimated based on multivariable regression, where all relevant participant characteristics were included in the model (Elze et al. 2017). Unlike reweighting methods, regression models require a large sample (or in context of time to event endpoints, a large number of events) compared to the number of prognostic variables.

All statistical analyses and graphical interpretation of the results were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina), and R version 3.6.1 and 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). IPTW and propensity score matching methods are recognized by health technology assessment bodies such as NICE to analyze comparative IPD from non-randomized studies (Faria et al. 2015).

C.1.5 Weighting

The propensity score is a balancing score defined by Rosenbaum and Rubin as the probability of treatment assignment conditional on observed baseline prognostic variable: ei = Pr(Zi = 1|Xi) (Rosenbaum and Rubin 1983). IPTW uses the propensity score to remove the effects of confounding when estimating the effects of treatment on the outcome. Propensity scores were derived with a multivariable logistic regression using each cohort (MonumenTAL-1 versus MajesTEC-1) as the dependent variable and selected baseline prognostic variables as explanatory factors. The estimated propensity scores were then used to derive weights for each participant using weighting formulas for the desired target population.

Following weighting, balance between the MonumenTAL-1 cohort and the MajesTEC-1 cohort was evaluated by comparing unweighted and weighted propensity score distributions, as well as unweighted and weighted SMD plots for the MonumenTAL-1 cohort, with SMD ≤0.20 indicating balance between both cohorts (Figure 23) (Austin 2009).

C.1.6 Target populations

The current analysis estimated the ATC population. The weights for participants in the MajesTEC-1 cohort were $\widehat{ATCw}_{0k}$ =1 ($k = 1, 2, \cdots, n_0$), and the weight for participants in MonumenTAL-1 with a propensity score, $\tilde{p}_{1k}$, were $\widehat{ATCw}_{1k} = u\widehat{ATCw}_{1k} \times n_0/sum(u\widehat{ATCw}_{0k})$ ($k = 1,2, \cdots, n_1$), where $u\widehat{ATCw}_{1k} = (1 - \tilde{p}_{1k})/\tilde{p}_{1k}$ is the unscaled ATC weight, and n_1 and n_0 were the sample sizes for the MajesTEC-1 and the MonumenTAL-1 cohort, respectively (Li et al. 2018). A sensitivity analysis estimating the ATT was conducted where the weights for participants in the MonumenTAL-1 cohort were $\widehat{ATTw}_{1k}$ =1 ($k = 1, 2, \cdots, n_1$), and the weight for participants in MajesTEC-1 with a propensity score, $\tilde{p}_{0k}$, were $\widehat{ATTw}_{0k} = u\widehat{ATTw}_{0k} \times n_0/sum(u\widehat{ATTw}_{0k})$ ($k = 1,2, \cdots, n_0$), where $u\widehat{ATTw}_{0k} = \tilde{p}_{0k}/(1 - \tilde{p}_{0k})$ is the unscaled ATT weight, and n_1 and n_0 were the sample sizes for the MonumenTAL-1 and the MajesTEC-1 cohort, respectively (Li et al. 2018).

C.1.7 Estimating adjusted treatment effect

The comparative effectiveness of talquetamab versus teclistamab was determined in terms of ORR, CR or better rate, VGPR or better rate, DOR, PFS, TTNT, and OS. Estimates of comparative effectiveness were derived for both the unadjusted comparison (i.e., talquetamab versus teclistamab prior to IPTW), and the adjusted comparison (i.e., with IPTW). For the binary outcomes (e.g., ORR, CR or better rate, and VGPR or better rate), a weighted logistic regression was used to estimate Odds Ratio's (OR), Response ratio's (RR), and Risk Differences (RD) with the respective 95% CI, transformed to RR. For the time-to-event outcomes (e.g., DOR, PFS, TTNT, and OS), a weighted Cox proportional hazards model was used to estimate HRs and respective 95% CIs.

C.1.8 Assessment of proportional hazards

Appropriateness of the proportional hazards assumption for survival outcomes was assessed based on visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals plot, and performance of the Grambsch-Therneau test (Grambsch and Therneau 1994) (with a p-value less than 0.05 considered to indicate the assumption does not hold). If there is clear evidence that the proportional hazards assumption does not hold, we will consider methods to account for time-varying hazards as opposed to Cox proportional-hazards models (Zhao et al. 2016).

C.1.9 Assessment of unmeasured confounding

To assess the potential impact of unmeasured confounding, E-values (VanderWeele and Ding 2017) for key outcomes were calculated. The E-value is defined as the minimum strength of association on the risk ratio scale that confounders would need to have with both the exposure (i.e., treatment group) and the outcome, conditional on the measured covariates, to fully explain away an observed exposure–outcome association. The calculation of E-value makes no assumptions on the scale and distribution of the outcomes (Mathur et al. 2018). E-value will be calculated based on the observed relative measures, i.e., response-rate ratio for ORR and hazard ratio for time-to-event outcomes.

C.1.10 Multivariable regression models as sensitivity analyses

Model specifications

Multivariable regressions were conducted including a binary treatment indicator (talquetamab or teclistamab) and baseline prognostic variables for adjustment in the model.

Estimating adjusted treatment effect

The comparative effectiveness of talquetamab versus teclistamab was determined in terms of ORR, CR or better rate, VGPR or better rate, DOR, PFS, TTNT, and OS. For the binary outcomes (eg, ORR, CR or better rate, and VGPR or better rate), an unweighted logistic regression including the selected baseline characteristics as prognostic variables was used to estimate the OR, RR and RD with the respective 95% CIs. For the time-to-event outcomes (eg, DOR, PFS, TTNT, and OS), an unweighted Cox proportional hazards model including the selected baseline characteristics as prognostic variables was used to estimate the HR and its respective 95% CI. The variance was estimated using a robust sandwich variance estimator (Li et al. 2018). For all time-to-event analyses, observed and weighted survival curves were reported, including the number of participants at risk across time.

C.1.11 Propensity score matching

Additional sensitivity analyses covering propensity score matching using optimal matching algorithm were performed. The optimal matching algorithm is a matching without replacement algorithm that forms matched pairs to minimize the average within-pair difference in propensity scores and has been shown to reduce bias (Austin 2014). All analyses were conducted for each of the outcomes listed in Section 3.7.1 (ORR, CR or better rate, VGPR or better rate, DOR, PFS, TTNT, and OS).

Appendix E. Serious adverse events

E.1 Safety Results for RP2D at 0.8 mg/kg Q2W (Phase 1 and Phase 2 Cohort C)

E.1.1 Serious Adverse Events

Among patients who received talquetamab at the RP2D of 0.8 mg/kg Q2W SC (Phase 1 and Phase 2 Cohort C; January 17, 2023 clinical cut-off), 70 (48.3%) had at least one serious TEAE reported (Table 76) (Janssen 2023h). The most frequently reported (≥2%) serious TEAEs were CRS (10.3%), pyrexia (4.8%), ICANS (3.7%), COVID-19 (3.4%, and syncope (2.1%).

Table 76. Summary of serious TEAEs reported in ≥2% of patients in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023cut-off)

Serious TEAE	n (%)		
	Phase 1 n = 36	Phase 2 Cohort C n = 109	Total n = 145
Number of Patients with ≥1 Serious TEAEs	12 (33.3%)	58 (53.2%)	70 (48.3%)
Infections and Infestations	1 (2.8%)	22 (20.2%)	23 (15.9%)
COVID-19	0	5 (4.6%)	5 (3.4%)
Immune System Disorders	2 (5.6%)	13 (11.9%)	15 (10.3%)
CRS	2 (5.6%)	13 (11.9%)	15 (10.3%)
General Disorders and Administration Site Conditions	1 (2.8%)	7 (6.4%)	8 (5.5%)
Pyrexia	1 (2.8%)	6 (5.5%)	7 (4.8%)
Nervous system disorders	4 (11.1%)	9 (8.3%)	13 (9.0%)
ICANS	-	4 (3.7%)	-

Note: Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using MedDRA version 24.1.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
Note: Percentages were calculated with the number of patients in the All Treated Analysis Set as the denominator.
Note: AEs are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.
Note: ICANs were only collected for phase 2.
Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; MedDRA = Medical Dictionary for Regulatory Activities; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; TEAE = treatment emergent adverse event.
Source: Janssen (2023h).

E.1.2 Cytokine Release Syndrome

One hundred eight (108 [74.5%]) CRS events were reported in the 0.8 mg/kg Q2W SC cohort, of which just one Grade 3 or 4 event (0.7%) occurred (Schinke et al. 2023, Janssen 2023h). Multiple occurrences of CRS were reported in 46 patients (31.7%), with 6 patients (4.1%) having their toxicity grade worsen at subsequent CRS event. Most CRS events occurred during step-up dosing (Step-up Dose 1: 26.2%; Step-up Dose 2: 40.7%; Step-up Dose 3: 34.5%) or the first treatment cycle (Dose 1 Day 1: 13.1%; Dose 1 Day 15: 4.8%); just five patients (3.4%) experienced CRS in Cycle 2 of treatment or later, as did three patients (2.1%) during the repeat step-up dose. The median time from the last dose of talquetamab to onset of CRS was two days (range: 1 to 15) and the median duration of CRS events was two days (range: 1 to 29). At least one symptom of CRS was reported for 108 patients (74.5%).

The most common symptom of CRS was pyrexia (73.8%) and the maximum severity of most symptoms of CRS was Grade 1 or 2. Supportive measures to treat CRS or its symptoms were administered to 103 patients (71.0%); these treatments included paracetamol (77 [53.1%]) and tocilizumab (55 [37.9%]), including 2 patients (1.4%) who received >1 dose of tocilizumab for a single CRS event. All CRS events were recovered or fully resolved at the January 17, 2023 cut-off, and only one patient discontinued treatment owing to the development of CRS (Grade 1 event started at Cycle 3 Day 1, resolved after single dose of tocilizumab and discontinuation of study drug). Treatment-emergent CRS events and CRS-related supportive measures are presented in Table 77.

Table 77. Treatment-emergent CRS events and CRS-related supportive measures in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)

CRS Event/Category	Phase 1 n = 36	Phase 2 Cohort C n = 109	Total n = 145
Number of patients with CRS, n (%)	29 (80.6%)	79 (72.5%)	108 (74.5%)
Maximum toxicity grade, n (%)			
Grade 1	22 (61.1%)	61 (56.0%)	83 (57.2%)
Grade 2	7 (19.4%)	17 (15.6%)	24 (16.6%)
Grade 3	0	1 (0.9%)	1 (0.7%)
Grade 4	0	0	0
Grade 5	0	0	0
Number of patients with serious CRS, n (%)	2 (5.6%)	13 (11.9%)	15 (10.3%)
Number of patients with multiple CRS events, n (%)	7 (19.4%)	39 (35.8%)	46 (31.7%)
Grade of CRS worsened at any subsequent event	1 (2.8%)	5 (4.6%)	6 (4.1%)
Time from last injection of talquetamab to onset of CRS (days)			
Number of CRS events	42	147	189
Mean (SD)	2.2 (0.68)	2.5 (1.66)	2.4 (1.50)
Median (range)	2.0 (1, 5)	2.0 (1, 15)	2.0 (1, 15)
Duration of CRS (days)[a]			
Number of CRS events	42	147	189
Mean (SD)	2.1 (0.93)	3.0 (4.11)	2.8 (3.67)
Median (range)	2.0 (1, 5)	2.0 (1, 29)	2.0 (1, 29)
Number of patients with CRS leading to discontinuation of talquetamab	0	1 (0.9%)	1 (0.7%)
Occurrence of CRS[b], n (%)			
Step-up Dose 1	12 (33.3%)	26 (23.9%)	38 (26.2%)
Step-up Dose 2	10 (27.8%)	49 (45.0%)	59 (40.7%)
Step-up Dose 3	13 (36.1%)	37 (33.9%)	50 (34.5%)
Cycle 1 Day 1	3 (8.3%)	16 (14.7%)	19 (13.1%)
Cycle 1 Day 15	3 (8.3%)	4 (3.7%)	7 (4.8%)
Cycle 2+	0	5 (4.6%)	5 (3.4%)
Repeat Step-up	1 (2.8%)	2 (1.8%)	3 (2.1%)

CRS Event/Category	Phase 1 n = 36	Phase 2 Cohort C n = 109	Total n = 145
Patients with supportive measures to treat CRS, n (%)[c]	29 (80.6%)	74 (67.9%)	103 (71.0%)
Tocilizumab (anti-IL-6 receptor)	19 (52.8%)	36 (33.0%)	55 (37.9%)
Multiple doses at any time during study	3 (8.3%)	2 (1.8%)	5 (3.4%)
>1 dose for a single CRS event	0	2 (1.8%)	2 (1.4%)
Corticosteroids	2 (5.6%)	3 (2.8%)	5 (3.4%)
IV fluids	4 (11.1%)	21 (19.3%)	25 (17.2%)
Vasopressor used	0	1 (0.9%)	1 (0.7%)
Oxygen used	2 (5.6%)	8 (7.3%)	9 (6.2%)
Positive pressure	0	0	0
Paracetamol	17 (47.2%)	60 (55.0%)	77 (53.1%)
Other	10 (27.8%)	40 (36.7%)	50 (34.5%)
Outcome of CRS			
Number of CRS events	42	147	189
Recovered or resolved	42 (100.0%)	147 (100.0%)	189 (100.0%)
Not recovered or not resolved	0	0	0
Recovered or resolved with sequelae	0	0	0
Recovering or resolving	0	0	0
Fatal	0	0	0
Unknown	0	0	0
Missing	0	0	0

[a] Includes CRS events with both start and end dates available.
[b] Patients may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Supportive measures to treat CRS and CRS symptoms are included.
Note: Percentages were calculated with the number of patients in the All Treated Analysis Set as the denominator, except for the outcome of CRS for which percentages were calculated with the number of CRS events in the all-treated analysis set as the denominator.
Note: CRS was originally graded by Lee criteria (Lee et al. 2014) in Phase 1 and by ASTCT consensus grading system (Lee et al. 2019) in Phase 2, with conversion of grade in Phase 1 to ASTCT based on data in eCRF. Toxicity grade by ASTCT is presented in this table, for both Phase 1 and Phase 2 except for 1 patient in Phase 1 who had one CRS event each, which could not be converted to ASTCT criteria and is therefore reported by Lee criteria.
Note: AEs are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.
Note: Time from last injection to new onset is defined as date of last dose - start date of CRS + 1. Duration is defined as end date of CRS - start date of CRS + 1. For calculating in days, the date is used without time. For hours the date and time is used and those with time portion missing will be excluded.
Abbreviations: AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; eCRF = electronic case report form; IL = interleukin; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not available; Q2W = every two weeks; RP2D =

recommended Phase 2 dose; SC = subcutaneous; SD = standard deviation; TEAE = treatment emergent adverse event.
Source: Janssen (2023h).

E.1.3 Neurotoxicity Events

All-grade neurotoxicity events that were judged by the investigator to be related to talquetamab at the RP2D of 0.8 mg/kg Q2W SC were reported for 43 patients (29.7%) (see Table 78) (Janssen 2023h). Most neurotoxicity events were either Grade 1 or 2 in severity (36 patients [24.8% overall; 83.7% of patients with neurotoxicity events]), and six patients (4.1% overall; 14.0% of patients with neurotoxicity events) experienced a Grade 3 event. A total of 74 treatment-emergent neurotoxicity events occurred, with a median onset of 2.0 days (range: 1 to 28) from last dose of talquetamab and a median duration of 5.0 days (range: 1 to 321). Of the neurotoxicity events, 28.4% occurred concurrently with CRS (ie, the neurotoxicity event occurred during or within 7 days after the end date of CRS). At the time of the January 17, 2023 clinical cut-off, more than half of the neurotoxicity events were fully resolved (62.2%), and two patients (1.4%) discontinued treatment with talquetamab due to a neurotoxicity event (ICANS).

Table 78. Summary of treatment-emergent neurotoxic events and supportive measures in MonumenTAL-1 (Phase 1 and Phase 2 Cohort C; RP2D 0.8mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)

Neurotoxicity event	Phase 1 n = 36	Phase 2 Cohort C n = 109	Total n = 145
Number of patients with at least one neurotoxic event, n (%)	6 (16.7%)	37 (33.9%)	43 (29.7%)
Maximum toxicity grade, n (%)			
Grade 1	4 (11.%)	18 (16.5%)	22 (15.2%)
Grade 2	2 (5.6%)	12 (11.0%)	14 (9.7%)
Grade 3	0	6 (5.5%)	6 (4.1%)
Grade 4	0	1 (0.9%)	1 (0.7%)
Grade 5	0	0	0
Number of patients with serious neurotoxicity, n (%)	0	7 (6.4%)	7 (4.8%)
Number of patients with neurotoxicity leading to discontinuation of talquetamab, n (%)	0	2 (1.8%)	2 (1.4%)
Number of patients with multiple neurotoxicity events, n (%)	2 (5.6%)	16 (14.7%)	18 (12.4%)
Grade of neurotoxicity worsened at any subsequent event	1 (2.8%)	8 (7.3%)	9 (6.2%)
Patients with supportive measures to treat neurotoxicity events[a], n (%)	7 (19.4%)	25 (22.9%)	32 (22.1%)
Anakinra	0	1 (0.9%)	1 (0.7%)
Tocilizumab	4 (11.1%)	5 (4.6%)	9 (6.2%)
Haloperidol	0	0	0
Levetiracetam	0	2 (1.8%)	2 (1.4%)
Dexamethasone	1 (2.8%)	4 (3.7%)	5 (3.4%)
Gabapentin	0	1 (0.9%)	1 (0.7%)
Pregabalin	0	1 (0.9%)	1 (0.7%)
Other	5 (13.9%)	18 (16.5%)	23 (15.9%)
Occurrence of neurotoxicity[b], n (%)	1 (2.8%)	7 (6.4%)	8 (5.5%)
Step-up Dose 1	1 (2.8%)	8 (7.3%)	9 (6.2%)
Step-up Dose 2	0	7 (6.4%)	7 (4.8%)
Step-up Dose 3	0	9 (8.3%)	9 (6.2%)
Cycle 1 Day 1	2 (5.6%)	3 (2.8%)	5 (3.4%)

Neurotoxicity event	Phase 1 n = 36	Phase 2 Cohort C n = 109	Total n = 145
Cycle 1 Day 15	4 (11.1%)	15 (13.8%)	19 (13.1%)
Cycle 2+	0	2 (1.8%)	2 (1.4%)
Repeat Step-up			
Time from last injection of talquetamab to new onset of neurotoxicity (days)			
Number of neurotoxicity events			
Mean (SD)	10	64	74
	5.4 (6.57)	4.7 (5.63)	4.8 (5.72)
Median (range)	2.0 (1, 18)	2.0 (1, 28)	2.0 (1, 28)
Duration of neurotoxicity (days)[c]			
Number of neurotoxicity events			
Mean (SD)	8	42	50
	59.8 (108.17)	16.5 (27.89)	23.4 (50.79)
Median (range)	17.0 (1, 321)	4.0 (1, 133)	5.0 (1, 321)
Outcome of neurotoxicity, n (%)			
Number of neurotoxicity events			
Recovered or resolved	10	64	74
Not recovered or not resolved	8 (80.0%)	38 (59.4%)	46 (62.2%)
Recovered or resolved with sequelae	2 (20.0%)	20 (31.3%)	22 (29.7%)
Recovering or resolving	0	0	0
Fatal	0	2 (3.1%)	2 (2.7%)
Unknown	0	0	0
Missing	0	3 (4.7%)	3 (4.1%)
	0	1 (1.6%)	1 (1.4%)
Concurrent CRS[d], n (%)			
Yes			
No	1 (10.0%)	20 (31.3%)	21 (28.4%)
	9 (90.0%)	44 (68.8%)	53 (71.6%)

[a] Supportive measures to treat neurotoxicity and symptoms of ICANS are included.
[b] Patients may appear in more than one category; occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Includes AEs with both start and end dates available.
[d] Concurrent CRS considers neurotoxicity events that occur during or within 7 days of the end date of CRS.
Note: Percentages were calculated with the number of patients in the All Treated Analysis Set as the denominator, except for the concurrent events and outcome of neurotoxicity for which percentages were calculated with the number of neurotoxicity events in the All Treated Analysis Set as the denominator.
Note: Neurotoxicity events were graded according to the NCI-CTCAE Version 4.03, with the exception of ICANS, which were evaluated according to the ASTCT consensus grading system.
Note: AEs were reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.
Note: Neurotoxicity events are defined as AEs in the Nervous System Disorder SOC or Psychiatric Disorders SOC (excluding dysgeusia, ageusia, hypogeusia, taste disorder) that are considered related by investigator. Symptoms of CRS and ICANS are excluded.
Abbreviations: AE = adverse event; ASTCT=American society for transplantation and cellular therapy; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; SD = standard deviation; SOC = system organ class; TEAE = treatment emergent adverse event.
Source: (Janssen 2023e, Schinke et al. 2023)

Since ASTCT grading was not available for Phase 1, ICANS events were only described for Phase 2 (Part 3) of the study (see Table 79) (Janssen 2023h). Out of the 12 patients (11.0%) who received talquetamab at the RP2D 0.8 mg/kg Q2W SC and experienced an ICANS event, most events were Grade 1 or 2 in severity (8 [7.3%]), and 3 patients (2.8%) experienced a Grade 3 ICANS events. Multiple occurrences of ICANS events were reported for 2 patients (1.8%). ICANS events were restricted to early treatment, with all ICANS events occurring during either step-up dosing (Step-up Dose 1: 2.8%; Step-up Dose 2: 3.7%; Step-up Dose 3: 1.8%) or the first treatment cycle (Cycle 1 Dose: 3.7%), and

only one patient (0.9%) had any event of ICANS from the repeat step-up dose. The median time from the last dose of talquetamab to onset of ICANS event was 3.0 days (range: 2 to 16) and the median duration of ICANS was 1.0 days (range: 1 to 9). Ten out of the fifteen ICANS events (66.7%) occurred concurrently with CRS (ie, during or within seven days of resolution of CRS) and twelve events (80.0%) were recovered or resolved, including both of the Grade 3 ICANS events; one patient (0.9%) discontinued treatment due to ICANS. Supportive treatment was provided for nine patients (8.3%) with ICANS, and the most commonly used supportive measures were tocilizumab (4.6%) or dexamethasone (2.8%). Symptoms of ICANS that were reported for more than one patient were confusional state (4.6%), disorientation (1.8%), lethargy (1.8%), and somnolence (1.8%); no Grade 3 symptoms were reported for more than one patient. A symptom of ICANS was reported as a serious TEAE for one patient (0.9%; epilepsy).

Table 79. Summary of treatment-emergent ICANS events and supportive measures in MonumenTAL-1 (Phase 2 Cohort C; RP2D 0.8mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)

ICANS	Phase 2 Cohort C n = 109
Number of patients with ICANS, n (%)	12 (11.0%)
Maximum toxicity grade, n (%)	
Grade 1	4 (3.7%)
Grade 2	4 (3.7%)
Grade 3	3 (2.8%)
Grade 4	1 (0.9%)
Grade 5	0
Number of patients with serious ICANS, n (%)	4 (3.7%)
Number of patients with ICANS leading to discontinuation of talquetamab, n (%)	1 (0.9%)
Number of patients with multiple ICANS events, n (%)	2 (1.8%)
Grade of ICANS worsened at any subsequent event	0
Patients with supportive measures to treat ICANS events[a], n (%)	9 (8.3%)
Anakinra	1 (0.9%)
Tocilizumab	5 (4.6%)
Corticosteroids	3 (2.8%)
Dexamethasone	3 (2.8%)
Methylprednisolone sodium succinate	0
Levetiracetam	2 (1.8%)
Pethidine	0
Other	3 (2.8%)
Occurrence of ICANS[b]	
Step-up Dose 1	3 (2.8%)
Step-up Dose 2	4 (3.7%)
Step-up Dose	2 (1.8%)
Cycle 1 Day 1	4 (3.7%)
Cycle 1 Day 15	0
Cycle 2+	0
Repeat Step-up	1 (0.9%)
Time from last injection of talquetamab to new onset of ICANS (hours)	
≤12	2 (14.3%)
>12 to ≤24	4 (30.8%)
>24 to ≤48	4 (30.8%)
>48	14
Number of ICANS events	54.83 (88.619) 31.85 (5.4; 354.9)

ICANS	Phase 2 Cohort C n = 109
Mean (SD) Median (range)	
Time from last injection of talquetamab to new onset of ICANS (days) Number of ICANS events Mean (SD) Median (range)	 15 3.7 (3.54) 3.0 (2, 16)
Duration of ICANS (hours) Number of neurotoxicity events Mean (SD) Median (range	 12 29.89 (55.396) 7.79 (2.1, 193.7)
Duration of ICANS (days)[c] Number of ICANS events Mean (SD) Median (range)	 12 2.1 (2.35) 1.0 (1, 9)
Outcome of ICANS Number of ICANS events, n (%) Recovered or resolved Not recovered or not resolved Recovered or resolved with sequelae Recovering or resolving Fatal Unknown Missing	 15 12 (80.0%) 2 (13.3%) 0 0 0 1 (6.7%) 0
Concurrent with CRS[d] Yes No	 10 (66.7%) 5 (33.3%) Neurotoxicity events

[a] Supportive measures to treat ICANS and ICANS symptoms are included.
[b] Patients may appear in more than one category; occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred.
[c] Include ICANS with both start and end dates available.
[d] Concurrent CRS considers ICANS events that occur during or within 7 days of the end date of CRS.
Note: Percentages were calculated with the number of patients in the All Treated Analysis Set as the denominator, except for the concurrent events and outcome of ICANS for which percentages were calculated with the number of ICANS events in the All Treated Analysis Set as the denominator.
Note: Time from last injection to new onset is defined as date of last dose - start date of ICANS + 1. Duration is defined as end date of ICANS - start date of ICANS + 1. For calculating in days, the date is used without time. For hours the date and time is used and those with time portion missing will be excluded.
Note: AEs are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of talquetamab or until the start of subsequent anticancer therapy, if earlier.
Note: ICANs were only collected for phase 2.
Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; Q2W = every two weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; SD = standard deviation; TEAE = treatment emergent adverse event.
Source: Janssen (2023h).

E.1.4 Cytopenia

Cytopenias included neutropenia (all grades: 41 [28.3%]; Grade 3/4: 32 [22.1%]), anemia (66 [45.5%]; 40 [27.6%]), and thrombocytopenia (43 [29.7%]; 27 [18.6%]); these TEAEs were generally manageable (Schinke et al. 2023, Janssen 2023h). No patients experienced a Grade 5 cytopenia event or discontinued treatment due to cytopenia.

E.1.5 Infections

All-grade infection TEAEs were reported by 96 patients (66.2%), of whom 21 (14.5%) had ≥1 Grade 3 or 4 infection events and 2 patients (1.4%) experienced a Grade 5 infection (one COVID-19 pneumonia and one "infection" of unknown etiology) (Rasche et al. 2023, Schinke et al. 2023, Janssen 2023h). There were few opportunistic infections in the 0.8 mg.kg Q2W SC cohort (8 [5.5%]), all of which were Grade 1 or 2. Infection reported in at least 5% of patients were COVID-19 infection (34 patients [23.4%]), upper respiratory tract infection (13 [9.0%]), and pneumonia (9 [6.2%]). No patients had a TEAE of infection leading to discontinuation of talquetamab. In the 0.8 mg/kg Q2W SC cohort, 13.1% of patients received intravenous (IV) immunoglobulins (Igs) to manage infections. No decreases in CD19+ B-cell or polyclonal IgG levels were observed, supporting talquetamab as a B-cell-sparing treatment that allows maintenance of key elements of humoral immunity.

E.1.6 Skin Toxicities

Non-rash skin toxicity TEAEs (eg, skin exfoliation, dry skin, pruritus, and PPE) were reported in 106 patients (73.1%) treated with talquetamab 0.8 mg/kg Q2W SC (Schinke et al. 2023, Janssen 2023h). Nearly all events were low grade, with a maximum severity of Grade 1 and Grade 2 in 65 patients (44.8%) and 40 patients (27.6%), respectively; just one patient (0.7%) experienced a Grade 3 skin-related TEAE. The median time to onset from the initial step-up dose of talquetamab was 27 days (range: 1 to 595). Supportive measures were used in 39.3% of patients, with the most frequent interventions including triamcinolone acetonide (9.0%), ammonium lactate (8.3%), propylene glycol (6.2%), white soft paraffin (6.2%), and macrogol, simethicone, sorbic acid, or sorbitol (each 5.5%). Just one patient (0.7%) skipped a dose of talquetamab due to skin toxicity and two patients (1.4%) discontinued treatment due to a skin-related TEAE (dermatitis exfoliative generalized and dry skin).

Rash TEAEs were reported for 43 patients (29.7%) in the 0.8 mg/kg Q2W SC cohort, with a maximum severity of Grade 1 in 24 patients (16.6%), Grade 2 in 11 patients (7.6%), and Grade 3 in 8 patients (5.5%) (Schinke et al. 2023, Janssen 2023h). The median time to onset of rash TEAE from the initial step-up dose was 22 days (range: 1 to 379). Supportive measures were used in 22.1% of patients, including 13.8% and oral steroids in 4.8%; no individual medication was used in >5% of patients. Rash TEAEs rarely led to dose skips (3.4%), dose reductions (0.7%), or dose delays (0.7%), and no patients discontinued talquetamab due to a TEAE of rash. By the January 17, 2023 clinical cutoff, 72.3% of rash events had resolved, with a median duration of 26 days (range: 1 to 174).

E.1.7 Nail Toxicities

Nail disorder TEAEs were reported for 78 patients (53.8%), and the maximum severity was Grade 1 (68 [46.9%]) or Grade 2 (10 [6.9%]) (Janssen 2023h, Schinke et al. 2023). The median time to onset from the initial step-up dose was 67.5 days (range: 1 to 402). Various supportive measures were used by 11 patients (7.6%); no individual medication was used in >5% of patients. By the January 17, 2023 clinical cutoff, 25.5% of nail disorder events had resolved, with a median duration of 74 days (range: 14 to 388). No

nail disorder TEAEs led to dose skips, dose reductions, or dose delays and no patients discontinued study drug due to a TEAE of nail disorder.

E.1.8 Oral Toxicities

A total of 103 patients (71.0%) had a dysgeusia event, including 60 patients (41.4%) with a maximum Grade 1 event and 43 patients (29.7%) with a maximum Grade 2 event[4] (Janssen 2023h, Schinke et al. 2023). The median time to onset from the initial step-up dose was 15 days (range: 1 to 443) and supportive measures were used by 13 patients (9.0%), Of the 103 patients with dysgeusia, 17 patients (16.5%) had concurrent dry mouth and 12 patients (11.7%) had concurrent decreased appetite (ie, concurrent defined as during or within 30 days). Two patients (1.4%) discontinued treatment with talquetamab owing to the development of dysgeusia; 5 patients (3.4%) had a dose reduction, and 4 patients (2.8%) skipped a dose due to dysgeusia; no patients had a dose delay for dysgeusia TEAEs. By the January 17, 2023 clinical cut-off 30.8% of dysgeusia TEAEs had resolved, with a median duration of102 days (range: 15 to 504).

Fifty-eight patients (30.8%) treated with talquetamab 0.8 mg/kg Q2W SC reported a TEAE of dry mouth (Janssen 2023h). The maximum severity was Grade 1 in 39 patients (26.9%) or Grade 2 in 19 patients (13.1%). Supportive measures to treat dry mouth were used in 12.4% of patients. No patients discontinued talquetamab for a TEAE of dry mouth, 1.4% skipped a dose, and 2.1% had a dose reduction. By the January 17, 2023 clinical cut-off, approximately one-third (31.3%) of dry mouth events had resolved, with a median duration of 89 days (range: 1 to 317).

Decreased appetite was reported for 38 patients (26.2%) in the 0.8 mg/kg Q2W SC cohort (Janssen 2023h). These events were generally low grade (ie, Grade 1: 17.2%; Grade 2: 7.6%), with two Grade 3 decreased appetite TEAEs (1.4%). Supportive measures were used in 10 patients (6.9%). No patients discontinued study drug for a TEAE of decreased appetite, 2.1% skipped a dose, and 0.7% had a dose reduction. By the clinical cutoff, 42.1% of TEAEs of decreased appetite had resolved, with a median duration of 52 days (range: 3 to 334).

E.1.9 Weight Decreased

Sixty patients (41.4%) in the 0.8 mg/kg Q2W SC cohort reported a TEAE of weight decreased (Janssen 2023h). These events were generally low grade, with a maximum severity of Grade 1 in 15.2% of patients, Grade 2 in 20.7%, or Grade 3 in 5.5%. Most events of weight decreased occurred in Cycle 2 or later. Among the 60 patients with a TEAE of weight decreases, 14 (23.3%) had dysgeusia, 6 (10.0%) had dry mouth, and 5 (8.3%) had decreased appetite concurrently (or within 30 days of the end date of weight decreased). A TEAE of weight decreased led to dose reductions in 2.8% of patients, delayed dose in 0.7%, and skipped dose in 0.7%. One patient (0.7%) discontinued

[4] Note: As per the Common Terminology Criteria for Adverse Events (CTCAE), the maximum grade for dysgeusia is Grade 2.

talquetamab for a TEAE of weight decreased. By the clinical cutoff, 31.8% of weight decreased TEAEs had resolved, with a median duration of 58 days (range: 1 to 382).

E.2 Safety results for MajesTEC-1

Among patients who received teclistamab (Phase 1 and Phase 2 Cohort A; January 4, 2023 clinical cut-off), 68.5% had at least one serious TEAE reported (see **Error! Reference source not found.** below) (Janssen 2023e). The most frequently reported (≥2%) serious TEAEs were COVID-19 (20.6%), pneumonia (10.9%), CRS (8.5%), pyrexia (6.1%), general physical health deterioration (5.5%) and acute kidney injury (5.5%).

Table 80. Summary of serious TEAEs reported in ≥2% of patients in MajesTEC-1 (Phase 1 and Phase 2 Cohort A), All Treated Analysis Set (January 4, 2023 cut-off)

Serious TEAE	n (%)		
	Phase 1 n = 40	Phase 2 Cohort A n = 125	Total n = 165
Number of Patients with ≥1 Serious TEAEs	***21 (52.5%)***	***92 (73.6%)***	***113 (68.5%)***
Infections and Infestations	***13 (32.5%)***	***65 (52.0%)***	***78 (47.3%)***
COVID-19	5 (12.5%)	29 (23.2%)	34 (20.6%)
Pneumonia	5 (12.5%)	13 (10.4%)	18 (10.9%)
Pneumocystis jirovecii pneumonia	1 (2.5%)	5 (4.0%)	6 (3.6%)
Cellulitis	1 (2.5%)	3 (2.4%)	4 (2.4%)
General Disorders and Administration Site Conditions	***3 (7.5%)***	***20 (16.0%)***	***23 (13.9%)***
Pyrexia	1 (2.5%)	9 (7.2%)	10 (6.1%)
General physical health deterioration	2 (5.0%)	7 (5.6%)	9 (5.5%)
Immune system disorders	***2 (5.0%)***	***12 (9.6%)***	***14 (8.5%)***
Cytokine release syndrome	2 (5.0%)	12 (9.6%)	14 (8.5%)
Respiratory, thoracic and mediastinal disorders	***2 (5.0%)***	***12 (9.6%)***	***14 (8.5%)***
Hypoxia	0 (0.0%)	4 (3.2%)	4 (2.4%)
Musculoskeletal and connective tissue disorders	***2 (5.0%)***	***11 (8.8%)***	***13 (7.9%)***
Bone pain	0 (0.0%)	4 (3.2%)	4 (2.4%)
Blood and lymphatic system disorders	***2 (5.0%)***	***10 (8.0%)***	***12 (7.3%)***
Febrile neutropenia	1 (2.5%)	4 (3.2%)	5 (3.0%)
Neutropenia	0 (0.0%)	5 (4.0%)	5 (3.0%)
Gastrointestinal disorders	***3 (7.5%)***	***8 (6.4%)***	***11 (6.7%)***
Diarrhoea	1 (2.5%)	4 (3.2%)	5 (3.0%)
Renal and urinary disorders	***2 (5.0%)***	***9 (7.2%)***	***11 (6.7%)***
Acute kidney injury	2 (5.0%)	7 (5.6%)	9 (5.5%)
Psychiatric disorders	***2 (5.0%)***	***3 (2.4%)***	***5 (3.0%)***

Serious TEAE	n (%)		
	Phase 1 n = 40	Phase 2 Cohort A n = 125	Total n = 165
Confusional state	2 (5.0%)	2 (1.6%)	4 (2.4%)

Key: TEAE = treatment-emergent adverse event; RP2D = recommended Phase 2 dose; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

Note: Percentages calculated with the number of subjects in the all treated analysis set as denominator.

Note: Adverse events are reported until 100 days (Phase 1) or 30 days (Phase 2) after the last dose of teclistamab or until the start of subsequent anticancer therapy, if earlier.

Source: (Janssen 2023e)

Appendix F. Health-related quality of life

F.1 MonumenTAL-1

In Phase 2 of the MonumenTAL-1 trial, patient HRQoL was assessed at baseline, completion of the first treatment cycle, and then every other cycle until end of treatment using the following PRO instruments: the EORTC QLQ-C30, EQ-5D-5L, and the PGIS (Janssen 2023e).

The EORTC QLQ-C30 questionnaire was used to assess patient functioning and symptoms, such as pain, fatigue, and physical functioning, as well as overall HRQoL (Janssen 2023e). Scores range from 0 to 100, with higher scores indicative of better health on the global health status (GHS) and functional scales, and greater symptom severity on symptom scales. In total, 106 patients (97.2%) from the RP2D 0.8 mg/kg Q2W SC cohort completed the EORTC QLQ-C30 questionnaire at baseline.

Table 81. PRO scores at baseline in MonumenTAL-1 (Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)

PRO Scores at Baseline	PRO Population (n = 109)
EORTC QLQ-C30 score, mean (SD)	***N = 106***
GHS	59.12 (23.246)
Physical functioning	66.88 (24.055)
Role functioning	64.42 (30.197)
Emotional functioning	70.99 (22.160)
Cognitive functioning	79.56 (22.804)
Social functioning	68.41 (30.305)
Pain	37.46 (30.730)
Fatigue	43.81 (25.357)
Nausea and vomiting	5.82 (14.373)
Appetite loss	20.06 (26.130)
Constipation	11.64 (23.022)
Diarrhea	18.41 (28.860)
Dyspnea	21.07 (28.849)
Sleep disturbance	28.53 (28.413)
Financial difficulties	18.73 (28.089)
EQ-5D-5L score, mean (SD)	***N = 105***
Utility score	0.64 (0.272)
VAS	64.08 (20.510)T

Note: All the EORTC-QLQ-C30 scores are presented in the range of 0-100 after linear transformation from raw scores (in the range of 1-4). A higher score indicates better health on the global health and functional scales (physical, role, emotional, cognitive, and social) and greater symptom severity on the symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea).

Abbreviations: BCMA = B-cell maturation antigen; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L = EuroQol Five Dimension Five Level

Questionnaire; GHS = Global Health Status; PRO = patient-reported outcome; Q2W = every two weeks; SD = standard deviation; VAS = Visual Analogue Scale.
Source: (Janssen 2023e).

F.1.1 RP2D at 0.8 mg/kg Q2W (Phase 2 Cohort C)

F.1.1.1 EORTC QLQ-C30

Compliance for the EORTC QLQ-C30 was 96.3% at baseline and ranged from 82.9% to 92.3% for Cycles 1 through 15 (Janssen 2023e). Assessment of selected EORTC QLQ-C30 scales and change from baseline at Cycles 1 through 15 are presented below in Table 82. In alignment with the outcomes observed in the 0.4 mg/kg Q1W SC cohort, patients treated with talquetamab 0.8 mg/kg Q2W SC generally reported slight worsening in GHS, functioning, and MM symptoms after initiating step-up dosing and early treatment cycles (ie, Cycles 1 and 3); however, scores for EORTC QLQ-C30 subdomains improved relative to baseline with continued talquetamab treatment (ie, Cycles 5 through 15). Compared with baseline, mean scores for GHS decreased (ie, worsened) at Cycles 1 (-4.41 [24.505]) and 3 (-1.39 [23.736]), but increased (ie, improved) by Cycle 5 (3.80). By Cycle 15, patients in the 0.8 mg/kg Q2W SC cohort reported a mean change from baseline of 25.93 (15.278) in GHS, indicating that talquetamab 0.8 mg/kg Q2W SC is associated with improvements in overall health. Similarly, after an immediate worsening (ie, increase) of scores for fatigue at Cycles 1 and 3, patients treated with 0.8 mg/kg Q2W SC exhibited steady improvements in symptoms of fatigue, with a mean change of -19.75 (19.859) at Cycle 15 compared with baseline (ie, decreasing value is indicative of reduced fatigue). Patients also reported improvements in pain immediately after initiating talquetamab 0.8 mg/kg Q2W SC treatment, and experienced greater reductions in pain with prolonged treatment (ie, mean change from baseline of -0.56 [24.676] at Cycle 1 and -22.22 [26.352] at Cycle 15). Patients also reported improvements in several functioning domains within the first few treatment cycles, including physical functioning and role functioning. Adjusted LS mean changes from baseline to Cycle 15 generally showed improvements in several EORTC QLQ-C30 subscales, including GHS (11.50 [95% CI: 0.79, 22.18]), physical functioning (7 [-1.25, 15.31]), fatigue (-14.2 [-25.18, -3.19]), and pain (-19.1 [-31.18, -7.01).

Talquetamab was also associated with rapid improvements in overall health, functioning, and disease symptoms. Among the 0.8 mg/kg Q2W SC cohort, the median time to improvement (defined as increase in score that is at least half of standard deviation from baseline values) in GHS was 2.33 months, while the median time to improvement in several functioning (physical, emotional, cognitive, and social) and symptom domains (fatigue, pain, and nausea and vomiting) ranged from 0.53 to 2.39 months and 0.30 to 3.43 months, respectively (Janssen 2023e). Moreover, among the 90 patients who received talquetamab 0.8 mg/kg Q2W SC and had PRO data evaluable for meaningful improvement assessments, 19.3% experienced meaningful improvements in GHS at Cycle 1 Day 1, while 28.9% and 36.7% reported meaningful improvements in pain and fatigue, respectively. The proportion of patients with meaningful improvements in GHS and MM symptom scores generally increased with continued treatment; by Cycle 7, 33.3%, 38.3%, and 45.0% of patients reported clinically meaningful improvements in GHS, pain, and fatigue, respectively.

Table 82. Select summary of EORTC QLQ-C30 subscale scores and change from baseline at Cycles 1 through 15 in MonumenTAL-1 (Phase 2 Cohort C; RP2D 0.8 mg/kg Q2W SC), All Treated Analysis Set (January 17, 2023 cut-off)

	Measured Value				Change from Baseline		
	N	Mean	SD	Base Mean	N	Mean	SD
GHS							
Baseline	106	59.12	23.246				
Cycle 1 Day 1	88	54.73	22.630	59.00	87	-4.41	24.505
Cycle 3 Day 1	72	58.91	21.088	60.30	72	-1.39	23.736
Cycle 5 Day 1	68	63.11	16.748	59.31	68	3.80	23.851
Cycle 7 Day 1	60	63.19	21.768	59.72	60	3.47	27.715
Cycle 9 Day 1	57	64.77	22.877	61.99	57	2.78	27.292
Cycle 11 Day 1	39	70.09	21.092	60.26	39	9.83	24.548
Cycle 13 Day 1	24	59.03	26.113	57.64	24	1.39	29.659
Cycle 15 Day 1	9	75.93	20.175	50.00	9	25.93	15.278
Physical Functioning							
Baseline	106	66.88	24.055				
Cycle 1 Day 1	90	64.39	26.352	66.97	89	-2.83	18.244
Cycle 3 Day 1	73	67.81	22.988	67.70	73	0.11	19.579
Cycle 5 Day 1	68	70.82	22.116	66.80	68	4.02	19.021
Cycle 7 Day 1	60	71.47	22.405	67.04	60	4.44	19.864
Cycle 9 Day 1	59	70.03	24.452	69.08	59	0.95	20.109
Cycle 11 Day 1	39	71.05	22.631	67.24	39	3.82	16.769
Cycle 13 Day 1	24	65.37	24.360	59.17	24	6.20	21.305
Cycle 15 Day 1	9	78.52	18.791	65.19	9	13.33	11.055
Role Functioning							
Baseline	104	64.42	30.197				
Cycle 1 Day 1	90	54.81	33.263	65.34	88	-10.61	28.498
Cycle 3 Day 1	73	62.33	33.567	66.21	73	-3.88	30.747
Cycle 5 Day 1	68	68.14	29.889	64.18	67	4.23	22.908
Cycle 7 Day 1	60	67.50	31.357	66.10	59	2.26	22.839
Cycle 9 Day 1	57	67.84	30.023	67.56	56	0.89	28.501
Cycle 11 Day 1	39	70.09	27.354	66.23	38	4.82	22.894
Cycle 13 Day 1	24	62.50	33.783	57.25	23	6.52	31.277
Cycle 15 Day 1	9	70.37	29.788	62.96	9	7.41	22.222
Pain Score							
Baseline	105	37.46	30.730				
Cycle 1 Day 1	90	35.37	31.881	36.14	89	-0.56	24.676
Cycle 3 Day 1	73	30.14	28.144	34.72	72	-4.17	24.980
Cycle 5 Day 1	68	28.68	27.597	35.32	67	-6.72	27.533
Cycle 7 Day 1	60	28.33	26.804	35.31	59	-6.50	26.081
Cycle 9 Day 1	58	27.59	27.845	35.06	58	-7.47	28.127
Cycle 11 Day 1	39	32.48	25.348	33.77	38	-1.32	21.358
Cycle 13 Day 1	22	37.88	35.702	40.15	22	-2.27	26.872
Cycle 15 Day 1	9	14.81	24.216	37.04	9	-22.22	26.352
Fatigue							
Baseline	105	43.81	25.357				
Cycle 1 Day 1	90	45.56	26.808	44.44	88	1.14	24.123
Cycle 3 Day 1	73	45.36	25.644	42.28	72	3.24	24.700
Cycle 5 Day 1	68	39.54	21.730	43.62	67	-3.98	22.469
Cycle 7 Day 1	60	38.06	24.395	43.69	59	-5.56	19.547
Cycle 9 Day 1	59	37.66	26.100	42.91	58	-4.98	24.198
Cycle 11 Day 1	39	37.04	19.963	43.86	38	-6.73	15.182
Cycle 13 Day 1	24	44.44	27.413	49.07	24	-4.63	24.059
Cycle 15 Day 1	9	25.93	18.426	45.68	9	-19.75	19.859

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; GHS = Global Health Status; Q2W = every other week; RP2D = recommended Phase 2 dose; SD = standard deviation.
Source: (Janssen 2023e).

F.1.1.2 EQ-5D-5L

Compliance for the EQ-5D-5L was 96.3% at baseline and ranged from 69.2% to 88.9% for post-baseline visits (ie, from Cycles 1 through 15) (Janssen 2023e). At baseline, the mean EQ-5D-5L VAS score was 64.08 (SD: 20.510) among the 115 patients who completed the EQ-5D-5L questionnaire in the 0.8 mg/kg Q2W SC cohort. After a slight decline in overall health status after initiating treatment (ie, Cycles 1 and 3), patients treated with talquetamab 0.8 mg/kg Q2W SC generally reported improvements in EQ-5D-5L VAS scores over the course of treatment, with mean VAS scores ranging from 66.64 (18.629) to 79.22 (15.943) from Cycles 5 through 15. Of note, one reduction in mean VAS score from baseline was reported at Cycle 13 (-0.57 [21.799]); however, the sample size is limited for later treatment cycles (ie, N = 24) and these results should be interpreted with caution. Patients in the 0.8 mg/kg Q2W SC cohort reported an adjusted LS mean change from baseline of 11.6 (95% CI: 0.9, 22.3) at Cycle 15, further indicating that overall health outcomes continued to improve with talquetamab therapy. The proportion of patients who achieved clinically meaningful improvements in VAS scores[5] increased with continued talquetamab 0.8 mg/kg Q2W SC treatment; at Cycle 1, 19.1% (17 of 89) of patients reported meaningful changes in VAS scores, which increased to 33.3% of patients (19 of 57) by Cycle 7. Finally, improvements in EQ-5D-5L VAS scores[6] occurred relatively quickly after initiating talquetamab therapy, with a median time to improvement of 2.79 months in the 0.8 mg/kg Q2W SC cohort.

Table 83 presents the time-dependent PF health state utility values and the single non-time-dependent PD health utility value, based on EQ-5D-5L questionnaires from patients in MonumenTAL-1 belonging to cohort C. The utilities were derived the Danish preference weight.

Table 83. Danish preference weights (based on HRQoL EQ-5D-5L), predicted by MMRRM

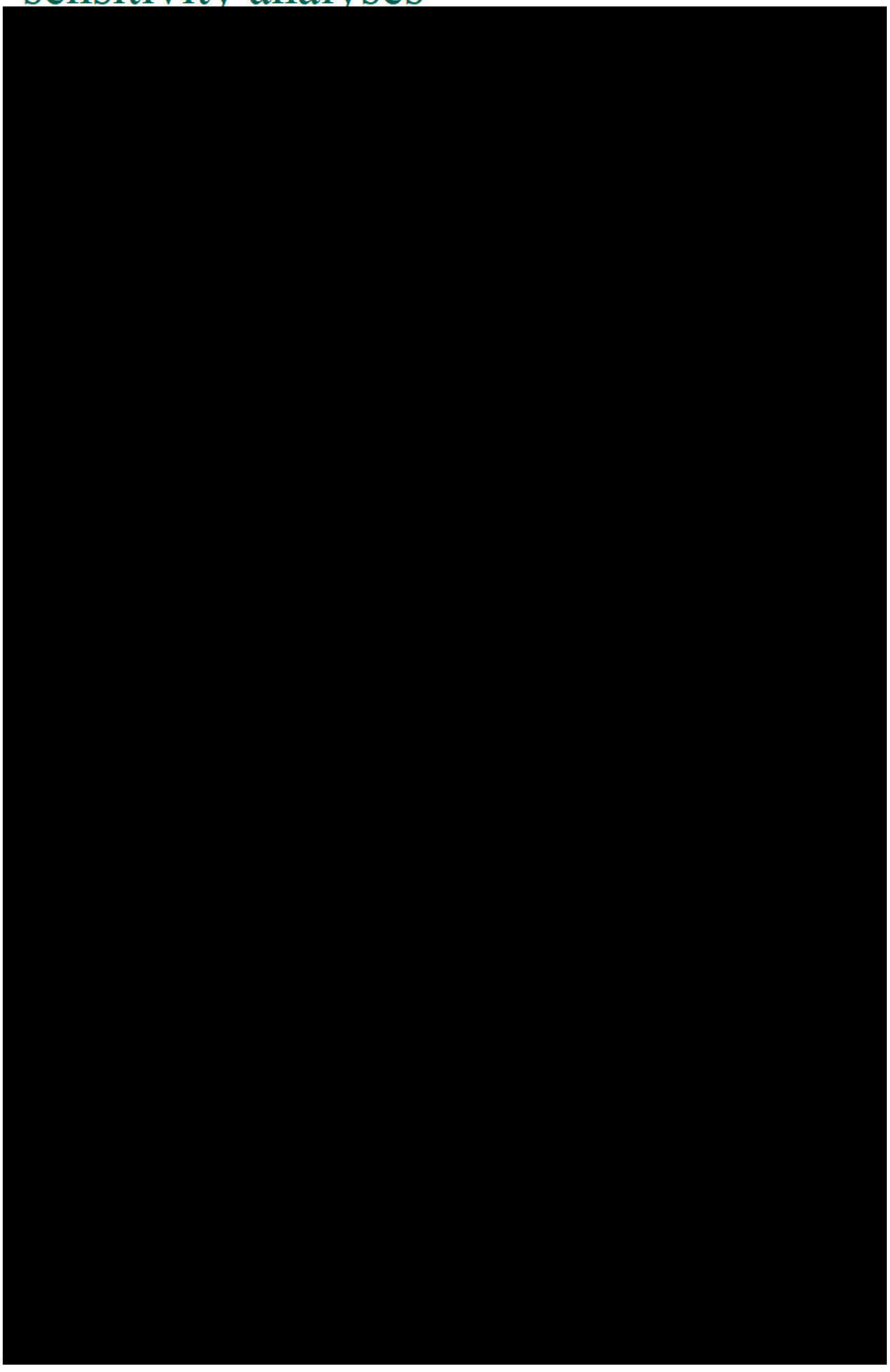
Talquetamab 0.8 mg/kg	
Time dependent PF utilities	
Baseline	0.703 (0.030)
Treatment cycle 1	0.718 (0.032)
Treatment cycle 3	0.763 (0.034)
Treatment cycle 5	0.812 (0.034)
Treatment cycle 7	0.801 (0.034)

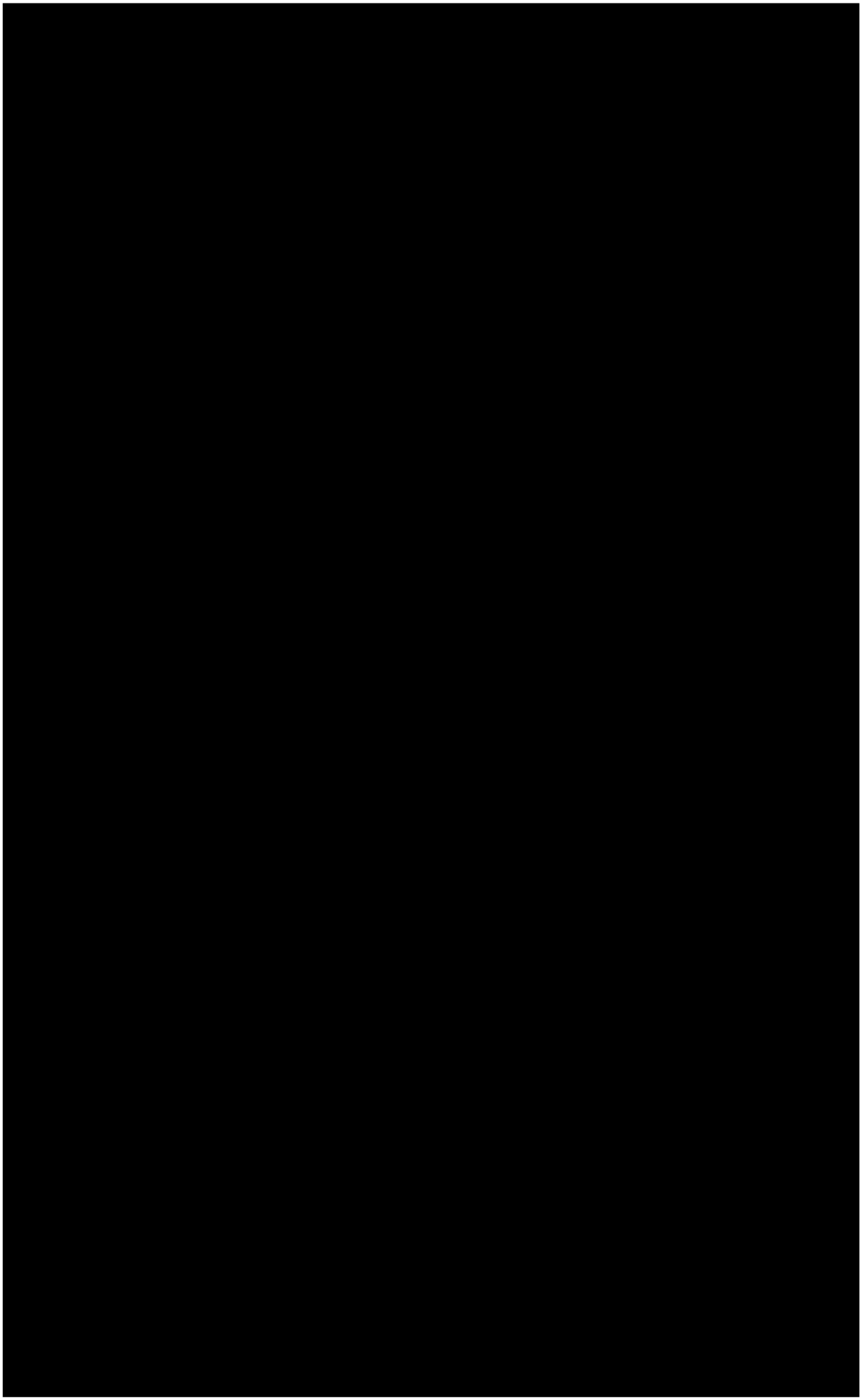
[5] The literature-based meaningful change threshold is 7 points for VAS scores.

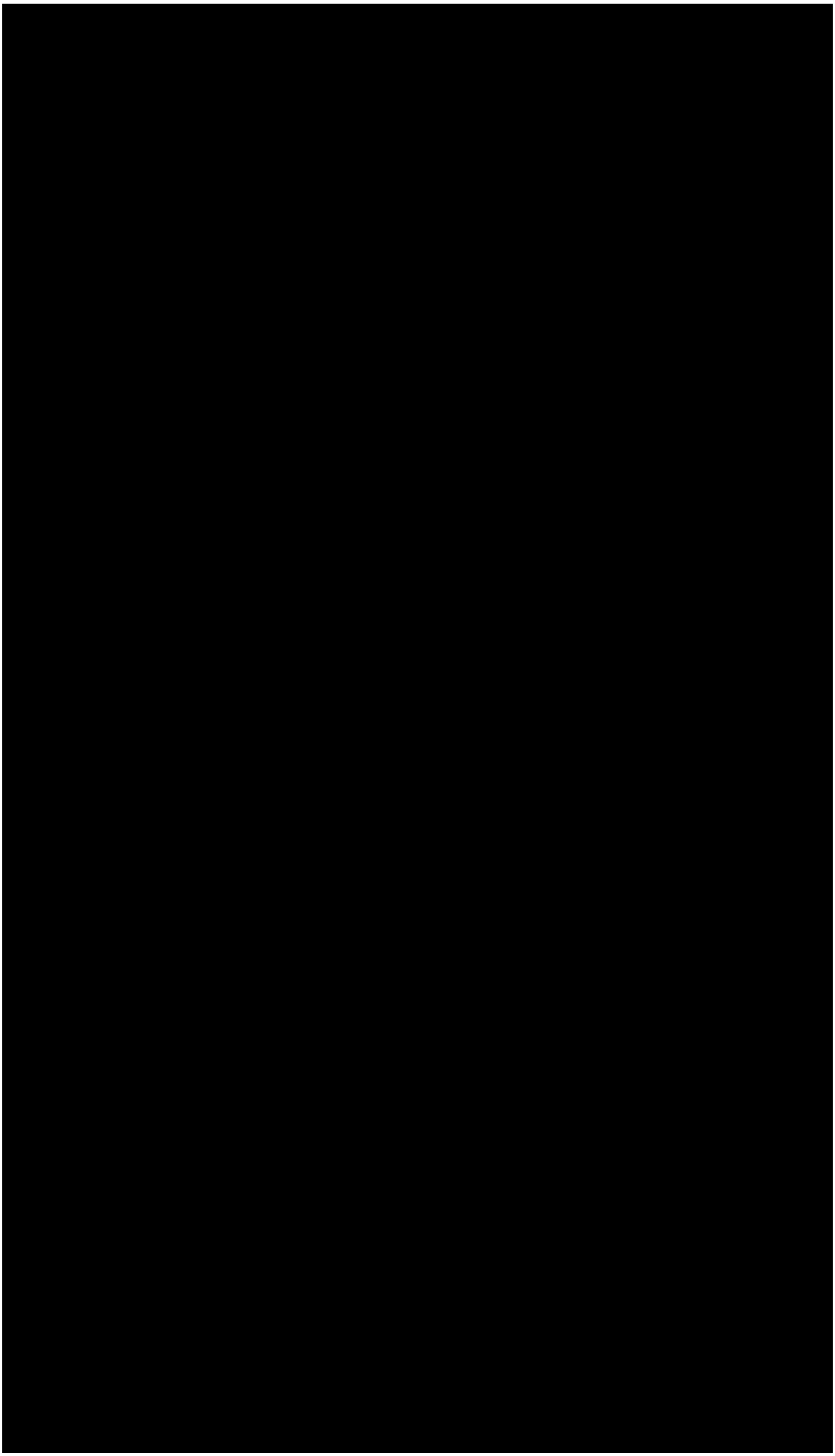
[6] Improvement in EQ-5D-5L scores is defined as an increase in score that is at least half of standard deviation from baseline values, where standard deviation is calculated from the scores at baseline.

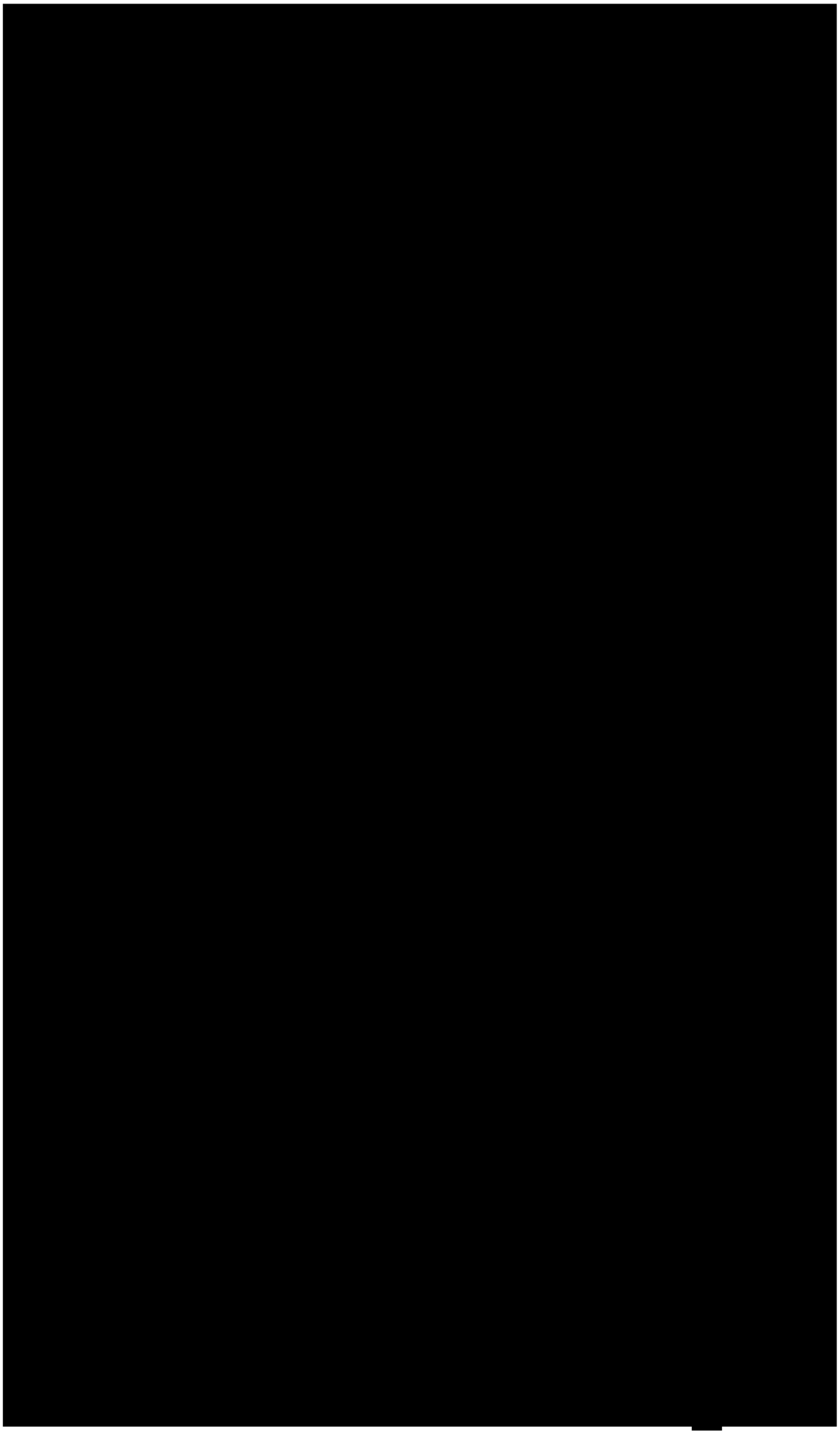
Treatment cycle 9	0.775 (0.035)
Treatment cycle 11	0.789 (0.040)
Treatment cycle 13	0.769 (0.051)
Treatment cycle 15	0.783 (0.103)
Treatment cycle 17	0.783 (0.103)
Treatment cycle 19	0.783 (0.103)
Treatment cycle 21	0.783 (0.103)
Progressed state	0.80 (0.039)

Appendix G. Probabilistic sensitivity analyses









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Appendix H. Literature searches for the clinical assessment

Literature searches for the clinical assessment

Not applicable. A systematic literature review is not applicable for this application comparing talquetamab and teclistamab. Janssen is the market authorization holder of teclistamab, in addition to talquetamab, and has therefore full knowledge of its pivotal trials. MajesTEC-1 is the only pivotal trial for teclistamab in treatment of triple-class exposed patients who have received at least three prior treatments. Additionally, regardless of indication, MajesTEC-1 is to date the only clinical trial based on which teclistamab has been granted market authorization within the European Union.

Appendix I. Literature searches for health-related quality of life

Not applicable.

Appendix J. Literature searches for input to the health economic model

Not applicable.

Appendix K. Mapping of health state utility values to Danish tariff

In the study by Jensen et al., composite time trade off (cTTO) and discrete choice (DC) tasks were conducted between October 2018 and November 2019 by study participants selected from the Danish adult population, to derive utility index values for 86 EQ-5D-5L health states. In the cTTO task, which combines TTO and lead-time TTO tasks, participants were asked to state their preference between 10 years in full health and 10 years in EQ-5D-5L health states. The time in full health state (x) was then reduced until the interviewee considered the two choices the same. The ratio of the reduced years to 10 years (x/10) gave the value of the health state. In case participants considered the health state worse than death, they were given the choice between '10 years in full health' and '10 years in full health plus 10 more years with the health state' and were asked to trade off '10 years in full health' (x) until the two options were deemed the same. In this case the value of the health state was considered to be (x-10)/10 (i.e. between -1 and 0). In the cTTO task, each participant evaluated one of the blocks of 10 EQ-5D-5L states, randomly selected from the 86 health states. Each block of 10 states included one mild state with four '1' scores and a single '2' score, eight moderate states, and the worst state (55555). In DC tasks, pairs of health states were shown to participants, and they stated their preference between each pair of health states. There was no time component in the DCE. Each participant was randomly assigned to one of 28 blocks of 7-pairs of health states (196 pairs of EQ-5D-5L states were used in the DC task).

The final sample included utility index values elicited from cTTO and DC tasks from 1041 participants, who were largely representative of the Danish adult population (based on Statistics Denmark 2018 data) in terms of gender, age (with an underrepresentation of 18- to 24-year-olds and over representation of 65- to 74-year-olds), marital status, and geographical region. The proportion with higher education in the sample was higher than the general population. Based on the utility index values for the EQ-5D-5L states elicited through cTTO and DC tasks, a conditional logit model for the DC data and a random-effects Tobit model for the cTTO data were combined in a 'heteroskedastic censored Tobit hybrid' model. The resulting model enables assigning utility index values, directly from EQ-5D-5L results (no mapping to 3L required), for each one of the 3,125 possible EQ-5D-5L results.

The coefficients presented in the Jensen article (Table 2 in the article) were used to assign a utility index to the EQ-5D-5L results observed in the trial. As a hypothetical example, if a patient's EQ-5D-5L assessment result was 23415, the utility index value for

this assessment was calculated as: 1 - 0.041 - 0.05 - 0.139 - 0 - 0.618 = 0.152. This value was then used in the estimation of health state utility values.

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