Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende teclistamab til behandling af patienter med knoglemarvs-kræft, som har fået mindst tre tidligere behandlingslinjer

Vers. 1.0

Bilagsoversigt

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

29. Januar 2024

Til Medicinrådet

Hermed Janssen-Cilags tilbagemelding på Medicinrådets udkast til vurdering af teclistamab til patienter med knoglemarvskræft

Vi ønsker at henlede opmærksomhed på to punkter forud for Rådets stillingtagen den 21. februar:

1. Plausibilitet af scenarie 2

I rapporten præsenteres to scenarier for sammenligningen af teclistamab og nuværende standardbehandling, *standard of care* (SOC). I scenarie 1 præsenteres effekten af teclistamab jf. vores antagelser vedr. fremskrivning af OS, PFS og TTD, mens i scenarie 2 præsenterer I effekten af jeres valgte, "*mere konservative omend klinisk plausible"*, fremskrivninger af OS, PFS og TTD.

Scenarie 1 betegner I som "*det optimistiske*". Jeres scenarie 2 betegner I som "*det konservative*". Valget af scenarie har en ikke-uvæsentlig betydning for omkostningseffektivitet og dermed jeres beslutningsgrundlag.

Vi forstår jeres tilgang med at præsentere et scenarie-spænd baseret på vurderingen af usikkerheden i de tilgængelige data. Dog ønsker vi at rejse spørgsmål ved den kliniske plausibilitet af scenarie 2. Er det realistisk, at tabet af livsår efter progression er dobbelt så stort som i scenarie 1? I scenarie 2 ekstrapolerer I OS for teclistamab-armen med en fordeling, der " *ligger blandt de tre pessimistiske kurver og estimerer en gennemsnitlig tid til progression på ca. 2,9 år*".

Medicinrådets metoder henviser til retningslinjerne fra NICE for korrekt sundhedsøkonomisk modellering. I scenarie 2 har I valgt forskellige parametriske modeller til de forskellige behandlingsarme med samme effektmål uden nærmere begrundelse. Det står i kontrast til retningslinjerne i NICE Technical Support Document 14[1].

Vi anerkender, at det er svært at vurdere den faktiske kliniske plausibilitet af de mulige ekstrapolerede kurver for teclistamab. Ikke desto mindre mener vi, at et mindst lige så plausibelt scenarie er, at patienter behandlet med teclistamab har en *bedre* post-progression overlevelse (PFS) sammenlignet med nuværende standardbehandling. Og såfremt vi også havde anvendt forskellige fordelinger i begge arme og ikke fulgt NICE retningslinjerne, ville dette være tilfældet.

Desuden er de valgte parametriske modeller i scenarie 2 blandt de dårligst tilpassede ifølge statistisk pasform (Akaikes informationskriterium (AIC)).

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[1] NICE TSD 14 https://www.sheffield.ac.uk/nice-dsu/tsds/full-list: "Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two-dimensional treatment effect in that the shape and scale parameters can both differ between 40 treatment arms but does not allow the modelled survival for each treatment arm to follow drastically different distributions[9]. If different types of models seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis."

Vi mener således, at der er flere faktorer, der berettiger et kritisk blik på plausibiliteten af scenarie 2.

Vi sætter derfor også pris på de steder i udkastet, hvor I skriver, at *fremskrivningen af OS - også i scenarie 1 - vurderes at være klinisk plausibel*. Baseret på ovenstående vil vi bede jer overveje rimeligheden af at beskrive dette tydeligere i den indledende opsummering og afsluttede diskussion. Vi ønsker dog absolut ikke en forsinkelse i processen pga. ovenstående forslag.

2. Real-world data af behandling med teclistamab

U/sikkerhed omkring effekt og sikkerhed ved behandling med teclistamab 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.

Vi ønsker at informere om nylig offentliggjorte real-world data fra 123 tyske patienter behandlet med teclistamab (Riedhammer 2024[2]). Disse data viser en sammenlignelig effekt og sikkerhedsprofil som i MajesTec-1 (ORR på 64,5% i BCMA-naiv gruppen vs. 63% i MAJESTEC-1), se figur 1. Dette til trods for at de inkluderede patienter havde en højere andel af høj-risiko parametre end i MajesTec-1 (EMD, ISS 3, mm) og/eller var forbehandlet med anti-BCMA regimer (ADC og CAR T). Sikkerhedsprofilen kunne ligeledes reproduceres i real-world analysen: Kun en lille del af patienterne udviklede grad 3 eller 4 CRS og ICANS (1,6 % og 0,8%). Risikoen for infektioner og cytopenier blev genfundet, men blev håndteret med adækvate interventioner.

[redacted]

Dette giver jer mulighed for systematisk at følge op på effekten af teclistamab efter en anbefaling, [redacted].

På vegne af Janssen

Madina Saidj, HEMAR Denmark, Janssen Pharmaceutical Company of J&J

[2] Riedhammer C, Bassermann F, Besemer B, et al. Real-world analysis of teclistamab in 123 RRMM patients from Germany. *Leukemia*. Published online January 20, 2024. doi:10.1038/s41375-024-02154-5

Figur 1 Real-world analysis of teclistamab in 123 RRMM patients from Germany (Riedhammer 2024)

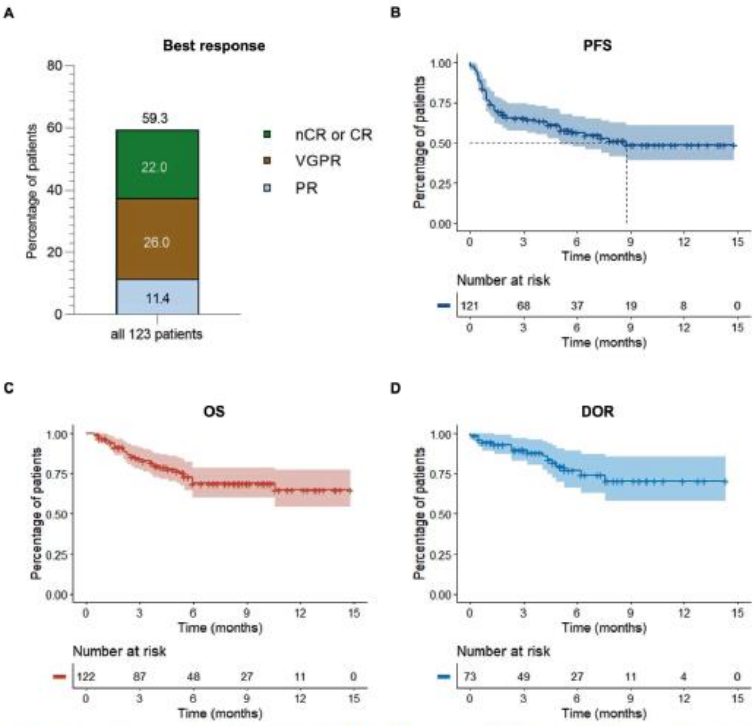

Fig. 1 Rate of response in 123 patients and Kaplan–Meier analysis of response duration and of progression-free and overall survival. Panel **A** shows the rates of near complete response and complete response (CR), very good partial response (VGPR), and partial response in 123 patients who were treated with teclistamab. Panel **B** illustrates progression-free survival and Panel **C** overall survival among the 123 patients. Panel **D** shows the duration of response to teclistamab therapy in the 73 patients who had an overall response (partial response or better). Tick marks indicate censored data. Bands indicate confidence bands around survival curves.

[redacted]

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25.01.2024

BMC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.02.2024
Leverandør	Janssen-Cilag
Lægemiddel	Tecvayli (teclistamab)
Ansøgt indikation	Tecvayli til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere behandlingslinjer
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Tecvayli (teclistamab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Tecvayli	10 mg/ml	3 ml	6.719,36	[redacted]	[redacted]	[redacted]
Tecvayli	90 mg/ml	1,7 ml	33.964,90	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros indgik en aftale på Tecvayli i december 2022, for at sikre, at patienter, som havde deltaget i kliniske afprøvninger, kunne fortsætte med at få behandlingen. Den nye pris, som Amgros har forhandlet, er betinget af en anbefaling fra Medicinrådet.

[redacted]

Konkurrencesituationen

Tecvayli er blandt de første bispecifikke antistoffer, som er vurderet i EMA, og som har opnået europæisk markedsføringstilladelse. Tecvayli er det er det første bispecifikke antistof til behandling af knoglemarvskræft i 4. linje, som bliver vurderet af Medicinrådet .

Der er flere bispecifikke antistoffer under behandling i EMA og Medicinrådet til behandling af knoglemarvskræft: Talvey (talquetamab) fra Janssen-Cilag, Lunsumio (mosunetusumab) fra Roche og Elrexfio (elranatamab) fra Pfizer. Den nøjagtige indikation ses i forbindelse med ansøgningerne til Medicinrådet.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tecvayli	10 mg/ml a 3 ml 90 mg/ml a 1,7 ml	Opstart: Dag 1: 0,06 mg/kg SC Dag 3: 0,3 mg/kg Dag 5: 1,5 mg/kg. Vedligeholdelsesdosis: 1,5 mg/kg SC 1 gang ugentligt	[redacted]	[redacted]
Tecvayli	10 mg/ml a 3 ml 90 mg/ml a 1,7 ml	Opstart: Dag 1: 0,06 mg/kg SC Dag 3: 0,3 mg/kg Dag 5: 1,5 mg/kg. Vedligeholdelsesdosis: 1,5 mg/kg SC 1 gang ugentligt Efter 6 måneder 1,5 mg/kg SC 1 gang hver 2. uge*	[redacted]	[redacted]

*For patienter med komplet respons eller bedre i mindst 6 måneder overvej at reducere doseringshyppigheden til 1,5 mg/kg SC hver anden uge jf. Medicinrådet vurderingsrapport
** Vægt 75 kg jf. Medicinrådets vurderingsrapport. En patient på 75 kg får som vedligeholdelsesdosis 112,5 mg per behandling og et hætteglas indeholder 153 mg. Lægemiddeludgifterne per år tager ikke højde for spild.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet		Link til anbefaling
Sverige	Under behandling		
England	Ikke igangsat	Afventer data	Link til anbefaling

Konklusion

Amgros vurderer, at leverandøren har givet deres bedst mulig pris.

Medicinrådet

Application for the assessment of TECVAYLI® (teclistamab) monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

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Table of contents

1. Basic information 6

2. Abbreviations 7

3. Tables and Figures 11
3.1 List of tables 11
3.2 List of figures 13

4. Summary 16

5. The patient population, the intervention and choice of comparator(s) 17
5.1 The medical condition and patient population 17
5.1.1 Multiple Myeloma 17
5.1.2 Epidemiology 18
5.1.3 Patient populations relevant for this application 18

5.2 Current treatment options and choice of comparator(s) 19
5.2.1 Current treatment options 19
5.2.2 Prognoses 20

5.3 Choice of comparator(s) 22
5.3.1 Description of the comparator(s) 22

5.4 The intervention 24

6. Literature search and identification of efficacy and safety studies 26
6.1 Identification and selection of relevant studies 26
6.2 List of relevant studies 26
6.2.1 Relevant studies included in the assessment 26
6.2.2 Ongoing studies 27

7. Efficacy and safety 27
7.1 MajesTEC-1 27
7.2 LocoMMotion 28
7.3 Efficacy and safety – MajesTEC-1 results 28
7.3.1 Progression free survival 28
7.3.2 Overall survival 29
7.3.3 Overall response rate 30
7.3.4 Time to response 31
7.3.5 Duration of response 31
7.3.6 Switching to Q2W Dosing 33
7.3.7 Safety 33
7.3.8 Patient reported outcomes 34

7.4 Efficacy and safety – LocoMMotion results 35

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

7.4.1 Efficacy ... 35
7.4.2 Safety ... 37
7.4.3 Patient-reported outcomes ... 38

7.5 Comparative analyses of efficacy and safety ... 38
7.5.1 Method of synthesis ... 38
7.5.2 Results from head-to-head studies ... 39
7.5.3 Results from the comparative analysis ... 39
7.5.4 Safety results comparative analyses ... 51

8. Health economic analysis ... 52
8.1 Model ... 52
8.1.1 Model structure ... 52
8.1.2 Population ... 54
8.1.3 Intervention ... 54
8.1.4 Comparator ... 54
8.1.5 Outcomes ... 55
8.1.6 Perspective ... 55
8.1.7 Cycle length and half cycle correction ... 55
8.1.8 Time horizon ... 55
8.1.9 Discount rates ... 55
8.1.10 Uncertainty ... 55
8.1.11 Key assumptions used in the analysis ... 56
8.1.12 Limitations ... 56

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice ... 56
8.2.1 Presentation of input data used in the model and how they were obtained ... 56
8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice ... 58

8.3 Extrapolation of relative efficacy ... 61
8.3.1 Time to event data – overview ... 61
8.3.2 Progression free survival ... 62
8.3.3 Overall survival ... 66

8.4 Documentation of health-related quality of life (HRQoL) ... 73
8.4.1 Overview of health state utility values (HSUV) ... 73
8.4.2 Health state utility values used in the health economics model ... 76

8.5 Resource use and costs ... 77
8.5.1 Treatment costs ... 77
8.5.2 Wastage ... 78
8.5.3 Drug administration costs ... 78
8.5.4 Concomitant Medication ... 78
8.5.5 Subsequent Treatment Costs ... 78
8.5.6 Monitoring cost ... 79
8.5.7 Adverse events costs ... 79
8.5.8 End of life costs ... 80

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5.9 Non-medical costs ... 80

8.6 Results ... 80
8.6.1 Base case overview ... 80
8.6.2 Base case results ... 81

8.7 Sensitivity analyses ... 82
8.7.1 Deterministic sensitivity analyses ... 82
8.7.2 Scenario analysis ... 83
8.7.3 Probabilistic sensitivity analyses ... 84

9. Budget impact analysis ... 86
9.1 Number of patients ... 86
9.2 Budget impact ... 86

10. Discussion on the submitted documentation ... 87

11. List of experts ... 88

12. References ... 88

13. Appendix A Literature search for efficacy and safety of intervention and comparator(s) ... 95

14. Appendix B Main characteristics of included studies ... 96
14.1 Ongoing studies Teclistamab ... 100

15. Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety ... 102
15.1 Comparability of patients across studies ... 103
15.2 Comparability of the study populations with Danish patients eligible for treatment ... 103

16. Appendix D Efficacy and safety results per study ... 104
16.1 Results per study ... 107

17. Appendix E Safety data for intervention and comparator(s) ... 110

18. Appendix F Comparative analysis of efficacy and safety ... 111
18.1 Adjusted comparison ... 111
18.1.1 Data Sources and patient populations ... 111
18.1.2 Outcome ... 112
18.1.3 Methodology ... 112
18.1.4 Selection of Participants ... 116
18.1.5 Treatments Received Across all Eligible lines of treatment in the Physician's Choice Cohort ... 116
18.1.6 Identification and Rank Ordering of Prognostic Factors for Balancing ... 118
18.1.7 Balance of Populations in the Main Analysis and Sensitivity Analysis Including All Variables ... 120

19. Appendix G Extrapolation ... 126
19.1 Time to treatment discontinuation (TTD) ... 126

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

19.2 Administration Frequency Switch (AFS) 127

20. Appendix H Literature search for HRQoL data 130

21. Appendix I Mapping of HRQoL data 131

22. Appendix J Probabilistic sensitivity analyses 132

23. Appendix K Patient reported outcomes 135
23.1 MajesTEC-1 135
23.2 LocoMMotion 147

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

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Tecvayli®
Generic name	Teclistamab
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	N/A
Pharmacotherapeutic group	Oncology
Active substance(s)	teclistamab
Pharmaceutical form(s)	Teclistamab is a colorless to light yellow preservative-free solution for subcutaneous injection.
Mechanism of action	Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the CD3 receptor expressed on the surface of T cells BCMA, which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells [1]. With its dual binding sites, teclistamab is able to draw CD3+ T cells in close proximity to BCMA+ cells, resulting in T cell activation and subsequent lysis and death of BCMA+ cells, which is mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. This effect occurs without regard to T cell receptor specificity or reliance on major histocompatibility complex (MHC) Class 1 molecules on the surface of antigen presenting cells.
Dosage regimen	The recommended dosage of teclistamab is 1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule (see the Table below) below [1]. In addition, seen in MajesTEC-1, biweekly dosing can be applicable for a proportion of patients. Teclistamab should be continued until disease progression or unacceptable toxicity.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Teclistamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A

Teclistamab step-up dosing schedule

	Teclistamab dose	Dose schedule
Step-up dose 1	0.06 mg/kg	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

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Teclistamab is available as 10 mg/ml and 90 mg/ml solutions for injection. A 3 mL vial containing 30 mg of teclistamab (Strength: 10 mg/mL) A 1.7 mL vial containing 153 mg of teclistamab (Strength: 90 mg/mL)
Orphan drug designation	Pending

2. Abbreviations

Abbreviation / term	Definition
ADC	Antibody drug conjugate
AE	Adverse event
AFS	Administration Frequency Switch
AIC	Akaike information criterion
ALB	Serum albumin
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
ATO	Average treatment effect in the overlap
ATT	Average treatment effect in the treated
β2M	Serum β2 microglobulin
BCMA	B cell maturation antigen
BIC	Bayesian information criterion
BMI	Body mass index
BSA	Body surface area
CBR	Clinical benefit rate
CEAC	Cost effectiveness acceptability curve
CEM	Cost effectiveness model
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRAB	Hypercalcemia, renal failure, anemia, and bone disease
CRS	Cytokine release syndrome
CT	Computed tomography
d	Dexamethasone
D	Daratumumab
dL	deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRG	Diagnosis related group

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DVd	Daratumumab plus bortezomib plus dexamethasone
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC	European Organization for Research and Treatment of Cancer;
EQ-5D-5L	EuroQoL 5 Dimensions, 5 Levels
ERd	Elotuzumab plus lenalidomide plus dexamethasone
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FDA	Food and drug administration
18F-FDG	fluorodeoxyglucose F18
FISH	Fluorescence in situ hybridization
FLC	Serum free light chain
FUP-post	Follow-up visit on or after start of subsequent antimyeloma therapy
FUP-pre	Follow-up visit prior to start of subsequent antimyeloma therapy
g	grams
Gen	Generalised
GHS	Global health status
GLOBOCAN	Global Cancer observatory
HDAC	Histone deacetylase
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
ICD-10	International classification of disease version 10
ICER	Incremental cost effectiveness ratio
IgG4	Immunoglobulin G4
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
IPD	Individual patient-level data
IPTW	Inverse probability of treatment weighting
IRC	Independent review committee
IRd	Ixazomib plus lenalidomide plus dexamethasone
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous

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Kd	Carfilzomib plus dexamethasone
KME	Kaplan-Meier estimator
KOL	Key opinion leader
KRd	Carfilzomib plus lenalidomide plus dexamethasone
L	Liters
LDH	Lactate dehydrogenase
LOT	Lines of therapy
LSMeans	Least-Squares Means
LY	Life years
MA	Marketing authorisation
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
mDOR	Median duration of response
MGUS	Monoclonal gammopathy of undetermined significance
min	minutes
mL	milliliters
MM	Multiple myeloma
MMRM	Mixed-model repeated measures
mo	Months
mOS	Median overall survival
M protein	Monoclonal paraprotein
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTC	Mixed treatment comparison
NA	Not applicable
NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
NE	Not estimable
NGF	Next-generation flow cytometry
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Nobs	Number of observations
MR	Minimal response
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis

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PC	Physician's choice
PCd	Pomalidomide plus cyclophosphamide plus dexamethasone
Pd	Pomalidomide plus dexamethasone
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PI	Proteasome inhibitor
PICO	Patient population, Intervention, Comparator and Outcome
PO	Per oral
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PPP	Pharmacy purchase price
PPS	Post progression survival
PR	Partial response
PRO	Patient-reported outcomes
PRO-CTCAE	Patient-reported Outcomes Version of the Common Terminology Criteria for AE
PROMIS PF 8c	Patient-reported Outcomes Measurement Information System Short Form v2.0 - Physical Function 8c
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSP	Pharmacy selling price
QALY	Quality adjusted life years
QLQ-C30	Quality of Life Questionnaire Core-30
R	Lenalidomide
RCT	Randomized controlled trial
RD	Rate difference
rHuPH20	Recombinant human hyaluronidase PH20 enzyme
R-ISS	Revised ISS
RP2D	Recommended Phase 2 dose
RR	Response-rate ratio
RRC	Response review committee
RRMM	Relapsed/refractory MM
SAE	Serious AE
SC	Subcutaneous
sCR	Stringent CR
SD	Standard deviation
SE	Standard error
SMD	Standardized mean difference

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SMM	Smouldering multiple myeloma
SoC	Standard of care
SPC	Summary of product characteristics
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
STC	Simulated Treatment Comparison
SUV	Maximum standardized uptake value
tal	talquetamab
TEAE	Treatment-emergent adverse event
TEC	Teclistamab
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTR	Time to response
US	United States
V	Bortezomib
VAS	Visual Analogue Scale
VAT	Value added tax
VCd	Bortezomib plus cyclophosphamide plus dexamethasone
Vd	Bortezomib plus dexamethasone
VGPR	Very good partial response
Y	Yes

3. Tables and Figures

3.1 List of tables

Table 1. Base case result (discounted) 17
Table 2. Incidence and prevalence of MM in Denmark in 2016 - 2020 18
Table 3. Estimated number of patients eligible for treatment 18
Table 4. Baseline characteristics: MajesTEC-1 19
Table 5. Criteria for staging in MM ISS and R-ISS 20
Table 6. Physician's choice relevant for Denmark 22
Table 7. Summary of the combinations included as physician's choice 22
Table 8. Different teclistamab strengths 24
Table 9. Teclistamab step-up dosing schedule 25
Table 10. Packaging type, size and strength 25
Table 11. Relevant studies included in the assessment 26
Table 12. Progression-Free Survival based on Independent Review Committee Assessment; All Treated Analysis Set 28
Table 13. Overall survival; All Treated Analysis Set 29
Table 14. Overall best confirmed response rates for teclistamab in MajesTEC-1 30
Table 15. Descriptive Summaries for Time to Response based on Independent Review Committee Assessment; Responders in the All Treated Analysis Set (n = 165) 31

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 16. Duration of Response based on Independent Review Committee Assessment (Events Defined as Disease Progression or Death due to Any Cause); Responders in the All Treated Analysis Set (n=165) 32
Table 17. Overall Summary of Treatment-emergent Adverse Events; All Treated Analysis Set 33
Table 18. Most Common (≥5% in Total) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set 34
Table 19. Overview of efficacy results for physicians' choice 36
Table 20. Most Common (≥5% in Total) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term 38
Table 21 Mean changes from baseline in PROs for teclistamab vs RWPC 51
Table 22. Incidence rates of adverse events (Grade 3-4 in ≥5% of subjects unless other specified) 52
Table 23. Model structures in previous assessments in RRMM or MM 54
Table 24. Base case settings 56
Table 25. Summary of included clinical inputs 57
Table 26. Patient population 58
Table 27. Overview of intervention teclistamab 59
Table 28. Physician's choice treatment mix based on LocoMMotion, relevant for Denmark 59
Table 29. Overview of comparator physician's choice 60
Table 30. Summary of value 60
Table 31. Summary of relevance 61
Table 32. Goodness-of-fit statistics for the different survival models for progression free survival for teclistamab 63
Table 33. Proportion of patients progression free alive at landmark survival times for teclistamab and physician's choice 65
Table 34. Goodness-of-fit statistics for the different survival models for OS for teclistamab 68
Table 35. Proportion of patients alive at landmark survival times for teclistamab and physician's choice 71
Table 36. Summary table of the chosen parametric functions 72
Table 37. Undiscounted life years using the base case progression-free survival (PFS) distribution (lognormal) 73
Table 38. Time-dependent utilities in pre-progression state (based on mixed model for repeated measures [MMRM]) 74
Table 39. MajesTEC-1 Post progression index score 75
Table 40. Danish general population utility values stratified by age groups 75
Table 41. Summary of adverse event disutilities applied in the model 76
Table 42. Summary of intervention price 77
Table 43. Cost of physician's choice 77
Table 44. Drug administration costs 78
Table 45. Subsequent Treatment Mix 79
Table 46. Weekly resource use for routine follow-up care 79
Table 47. Cost of adverse events 80
Table 48. End of life costs 80
Table 49. Non-medical costs per health state (weekly) 80
Table 50. Base case overview 80
Table 51. Base case of the analysis 81
Table 52. Disaggregated utility results (discounted) 81
Table 53. Disaggregated cost results (discounted) 81
Table 54. OWSA – the 10 most influential model parameters 82
Table 55. Scenario analyses 83
Table 56. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced 86
Table 57. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced 86
Table 58 Expected budget impact of recommending the pharmaceutical for the current indication 86
Table 59. Main characteristics of the MajesTEC-1 study 96

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 60. Main characteristics of the LocoMMotion study 98
Table 61. Ongoing studies in patients with RRMM 100
Table 62. Baseline characteristics of patients in MajesTEC-1 and LocoMMotion 102
Table 63. Baseline characteristics of patients in MajesTEC-1 for the All Treated Analysis Set (n=165) and for the proportion that switched to Q2W dosing (n=63) 102
Table 64. Definition, validity and clinical relevance of included outcome measures 104
Table 65. Summary of main efficacy results for MajesTEC-1 107
Table 66. Summary of main efficacy results for LocoMMotion 108
Table 67. Treatment-emergent Adverse Events in ≥5% of participants by System Organ Class and Preferred Term (Total and Toxicity Grade of 3 or 4); LocoMMotion (n=248) 110
Table 68. Key Eligibility Criteria for MajesTEC-1 and Physician's Choice Cohorts 111
Table 69. Overview of Sensitivity Analyses 116
Table 70. Treatment Regimens in the LocoMMotion Physician's Choice Cohort (≥4 Patients). 117
Table 71. Final Ranking of Prognostic Factors and Availability in MajesTEC-1 and Physician's Choice Cohort 118
Table 72. Variable Description in MajesTEC-1 119
Table 73. Imputation of Missing Values in Selected Prognostic Factors 120
Table 74. Differences in Unadjusted Baseline Characteristics between ITT Populations from MajesTEC-1 and the Physician's Choice Cohort 121
Table 75. Overview of Group Demographic Balance Before and After Weighting 123
Table 76. Goodness-of-fit statistics for the different survival models for time to treatment discontinuation for teclistamab and PC 126
Table 77. Goodness-of-fit statistics for the different survival models for administration frequency switch for teclistamab 129
Table 78. Assumptions applied for probabilistic sensitivity analysis 132
Table 79. Number of patients complying withith EQ-5D-5L Assessment Over Time During Treatment during PFS (Phase 2 Cohort A; All Treated Analysis (January 2023 data cut)) 135
Table 80. Compliance with EORTC-QLQ-C30 Assessment Over Time During Treatment (Phase 2 Cohort A; all treated analysis set (January 2023 datacut) 135
Table 81. Summary of EQ-5D-5L Assessment and Change From Baseline Over Time in utility score and VAS, (Phase 2 Cohort A; All Treated Analysis Set) 137
Table 82. Summary of EORTC-QLQ-C30 Assessment and Change From Baseline Over Time (Phase 2 Cohort A) 139
Table 83. Summary of Compliance for PRO Assessments; All Treated Analysis Set 147
Table 84. Summary of Change from Baseline in EQ-5D-5L: Mixed Model for Repeated Measures; All Treated Analysis Set 147
Table 85. Summary of Change from Baseline in EORTC QLQ-C30 Assessments: Mixed Model for Repeated Measures; All Treated Analysis 147

3.2 List of figures

Figure 1. Trajectory of MM and RRMM—cycles of response, remission, and relapse in the presence of treatment and clonal evolution 17
Figure 2. Depth of response and their associated levels of malignant cells in MM 21
Figure 3. Change to current treatment algorithm 26
Figure 4. Kaplan-Meier Plot for Progression-Free Survival based on Independent Review Committee Assessment; All Treated Analysis Set 29
Figure 5. Kaplan-Meier Plot for Overall Survival; All Treated Analysis Set 30
Figure 6. Response and Follow-up Based on Independent Review Committee Assessment; Responders in the All Treated Analysis Set 31

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 7. Kaplan-Meier Plot for Duration of Response Based on Independent Review Committee Assessment (Events Defined as Disease Progression or Death due to Any Cause); All Responders and Responders with Schedule Change in the All Treated Analysis Set 32
Figure 8. Kaplan-Meier curve for progression-free survival based on Response Review Committee assessment 37
Figure 9. Kaplan-Meier curve for overall survival – LocoMMotion 37
Figure 10: Summary of Results for PFS 39
Figure 11. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of PFS for the main analysis 40
Figure 12. Log-Cumulative Hazards of PFS for the ITT Population; Main Analysis 41
Figure 13. Schoenfeld Residual Test for Treatment; PFS; for the ITT Population; Main Analysis 41
Figure 15. Summary of Results for OS 43
Figure 16. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of OS for the main analysis 43
Figure 17. Log-Cumulative Hazards of OS for the ITT Population; Main Analysis 44
Figure 18. Schoenfeld Residual Test for Treatment; OS; for the ITT Population; Main Analysis 44
Figure 20. Summary of Results for Response rates 46
Figure 21. Summary of Results for Overall response rates 46
Figure 22. Summary of results for ≥CR Rate 47
Figure 23. Summary of Results for ≥VGPR 48
Figure 24. Summary of Results for DoR 48
Figure 25. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of DoR for main analysis 49
Figure 26. Summary of Results for TTNT 49
Figure 27. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of TTNT for the main Analysis 50
Figure 28. PSM structure 52
Figure 29. Kaplan-Meier estimates for PFS in the ITT population from MajesTEC-1 (teclistamab) and LocoMMotion (physician's choice) 62
Figure 30. Log cumulative hazard and Schoenfeld residuals for progression free survival for teclistamab 63
Figure 31. All models overlayed on the Kaplan-Meier estimate for progression free survival in the teclistamab arm. 64
Figure 32. All distributions for progression free survival in the teclistamab arm, long-term projection 64
Figure 33. All models overlayed on the Kaplan-Meier estimate for progression free survival in the PC arm 65
Figure 34. All distributions for progression free survival in the PC arm, long-term projection 65
Figure 35. Base case progression free survival (PFS) extrapolations; teclistamab: lognormal; PC: lognormal 66
Figure 36. Kaplan-Meier estimates for OS in ITT population from MajestTEC-1 (teclistamab) and LocoMMotion (Physician's choice) 67
Figure 37. Diagnostic plots for overall survival for teclistamab and physician's choice 67
Figure 38. The best fitting distributions overlayed on the Kaplan-Meier estimate for overall survival in the teclistamab arm 68
Figure 39. The best fitting distribution for overall survival in the teclistamab arm, long-term projections 69
Figure 40. The best fitting distributions overlayed on the Kaplan-Meier estimate for overall survival in the physician's choice arm 69
Figure 41. The best fitting distribution for overall survival in the physician's choice arm, long-term projections 70
Figure 42. Hazard of death for all survival model distributions for teclistamab, MajesTEC-1 70
Figure 43. Hazard of death for all standard survival model distributions for physician's choice, LocoMMotion 71
Figure 44. Base case overall survival (OS) extrapolations; teclistamab: lognormal; PC: lognormal 72
Figure 45. Time dependent mean pre-progression utility values 74
Figure 46. Teclistamab Dosing Schedule 77
Figure 47. Tornado diagram 83
Figure 48. Cost-effectiveness plane 84
Figure 49. Cost-effectiveness acceptability curve 85
Figure 50. LocoMMotion trial design 98

Figure 51. Algorithm for selection of statistical techniques to compare treatments adapted from NICE TSD 113
Figure 52. Distributional Balance for the Unadjusted and Adjusted Main Analysis 114
Figure 53. Participant Selection Procedure based on key eligibility criteria 117
Figure 54. Balance of Covariates Before and After ATT Weighting in the ITT Population for the Main Analysis 125
Figure 55. The best fitting distributions for time to treatment discontinuation in the teclistamab arm, overlayed with the PFS lognormal survival model 126
Figure 56. The two best fitting distributions overlayed on the PFS model of lognormal for time to treatment discontinuation in the physician's choice arm 127
Figure 57. All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (one-year time-horizon). 128
Figure 58. All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (two-year time-horizon). 128
Figure 59 All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (40-year time-horizon)..... 129
Figure 60. AFS base case (Teclistamab)..... 130

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4. Summary

Teclistamab (Tecvayli®) is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMid), and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy, hereafter referred to as triple class exposed. The target population for this assessment consists of adult Danish patients with RRMM that are triple class exposed. RRMM is defined as MM which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy.

Triple class exposed RRMM represents a patient subset that has aggressive disease and particularly poor survival outcomes with median overall survival (mOS) with conventional therapies ranging from only 8.2 to 15.7 months. Patients with RRMM have a substantial symptom burden, resulting in worse functioning and well-being than patients with new or stable disease. Survival, health-related quality of life (HRQoL), and physical functioning decrease substantially with each subsequent line of therapy, resulting in especially poor outcomes and a high burden for patients who fail multiple lines of standard therapy. Notably, low response rates are the key contributing factor for a rapid decline in OS. As of now, there is no clear treatment paradigm and few effective treatment options are available for that heavily pre-treated patient group.

Tecvayli® (teclistamab) is a humanized immunoglobulin G4 (IgG4) bispecific antibody targeting the B cell maturation antigen (BCMA). Tecvayli® is indicated for the treatment of adult patients with RRMM who have received at least three prior therapies including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy], hereafter referred to as triple-class exposed.

Safety and efficacy of teclistamab is evaluated in MajesTEC-1 (a single-arm, open-label, multi-centre, phase 1/2 study [NCT04557098]), that included: safety, progression-free survival (PFS), overall survival (OS), and response rates amongst other endpoints. In MajesTEC-1 teclistamab provided a high overall response rate (ORR) of 63.0% (95% CI: 55.2 to 70.4) among heavily pre-treated patients with triple class exposed RRMM. Response to teclistamab was durable and deepened over time, among all responders, including 63 subjects who had received Q2W dosing, median duration of response (DOR) was 21.6 months (95% CI: 16.2 to NE). Median time to best response was 4.0 months (range: 1.1 to 18.7). With a median follow-up of 22.8 months PFS (per IRC) was 11.3 months (95% CI: 8.8 to 16.4), and median OS was 21.9 months (95% CI: 15.1 to NE). Teclistamab is well tolerated, with a low rate of discontinuation 8 subjects (4.8%) due to treatment-emergent adverse events (TEAEs); TEAEs are effectively managed with available treatments. At least 1 Grade 3 or 4 TEAE was reported for 156 subjects (94.5%).

The current Danish treatment guidelines from DMC recommend a regimen containing carfilzomib or pomalidomide as fourth line treatment. Furthermore, due to patient heterogeneity, a regimen recommended in a prior line may also be considered in fourth line. The mentioned guidelines, however, do not include any specific treatment in the triple class exposed RRMM population, and treatment choice may depend on several factors. Hence, the most relevant comparator to teclistamab is a mix of currently available and used standard of care (SoC) regimens, hereafter called 'physician's choice', consisting of: Carfilzomib-dexamethasone (Kd), pomalidomide-dexamethasone (Pd) and pomalidomide-bortezomib-dexamethasone (PVd).

The comparator data used in this application are from the prospective LocoMMotion study. Comparative efficacy of teclistamab has not been assessed in any head-to-head clinical trials in participants with triple class exposed RRMM. In the absence of such head-to-head trials, adjusted comparisons based on individual patient data using inverse probability of treatment weighting (IPTW) methods have been performed to evaluate comparative efficacy between teclistamab (MajesTec-1) and the physician's choice (LocoMMotion).

In the adjusted comparison, teclistamab was associated with superior effectiveness among patients with triple class exposed RRMM compared with physician's choice for all outcomes. Teclistamab was associated with significantly higher odds of ORR (odds ratio [OR]: 4.89 [95% CI: 3.19, 7.47; P < 0.0001]; relative risk [RR]: 2.44 [95% CI: 1.79, 3.33]), and ≥CR rate (OR: 207.68 [95% CI: 28.21, 1528.90; P < 0.0001]; RR: 113.73 [95% CI: 15.68, 825.13]); than physician's choice and provide a significantly prolonged DoR (hazard ratio [HR]: 0.39 [95% CI: 0.24, 0.64; P = 0.0002]), compared with

physician's choice. Teclistamab was also associated with significantly prolonged PFS, compared with physician's choice PFS (HR: 0.48 [95% CI: 0.35, 0.64; P < 0.0001]) and was associated with prolonged OS, compared with physician's choice OS (HR: 0.64 [95% CI: 0.46, 0.88; P = 0.0055]). The difference in OS is expected to become statistically significant as data matures. This expectation is based on the established relationship between depth of response and prolonged survival.

To determine the cost effectiveness of teclistamab compared to physician's choice for the treatment of adults with RRMM, a *de novo* cost-effectiveness model with a partitioned survival model (PSM) structure was adapted to the Danish setting. The outcomes from the analysis included total costs as well as treatment benefits measured by life years (LYs) and quality adjusted life years (QALYs) gained from a Danish limited societal perspective. Furthermore, incremental differences were reported and summarized as incremental cost effectiveness ratios (ICERs). Severity was estimated with QALY shortfall.

Teclistamab was found to be more effective compared to physician's choice and more costly with an estimated ICER of 965,120 DKK based on list prices (Table 1).

Table 1. Base case result (discounted)

	Increment
Total life years	1.79
Total quality adjusted life years	1.36
Total cost (DKK)	1.778,478
ICER (DKK/QALY)	965,120

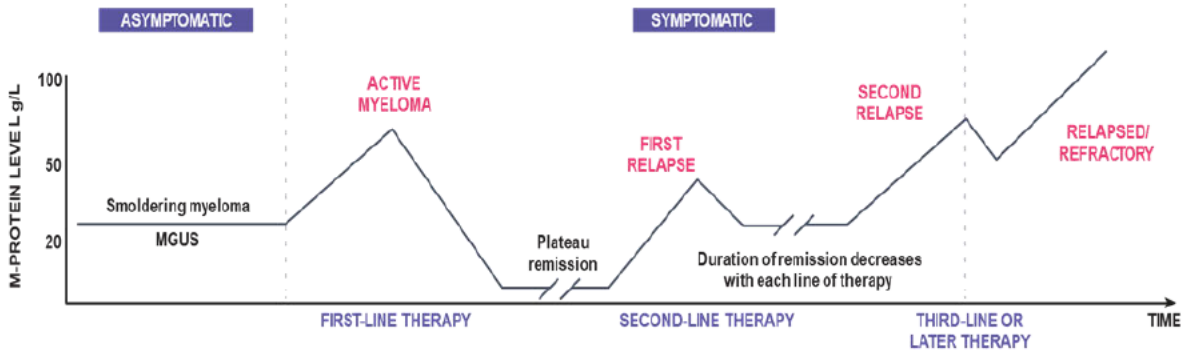
5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Multiple Myeloma

Multiple Myeloma (MM) is a rare and genetically complex hematological cancer [2] that forms in the plasma cells responsible for the production of antibodies and is characterized by the overproduction of M protein, an antibody, which can lead to bone lesions, increased susceptibility to infections, anemia, hypercalcemia, and renal insufficiency [2]. Due to the heterogeneity, MM can take a different clinical course in different patients, although the disease is typically characterized by multiple relapses, with patients becoming refractory to treatment over time [3] (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.
Note: Permission must be sought from the publisher before reproducing this figure for use with an external audience.
Source: Kurtin et al. [3].

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 [4].

Approximately 4% to 12% of MM patients are triple class exposed [5-7]. There are limited data on triple class-exposed RRMM, although the existing data point towards particularly poor prognosis [8, 9], and a high unmet need for effective therapies [10, 11]. As MM progresses, each subsequent line of therapy is associated with shorter progression-free survival (PFS) and a decreased rate, depth, and durability of response. With conventional therapies, median OS ranges from only 8.2 to 15.7 months [5, 12-14]. Only a few studies have evaluated long-term survival outcomes in this population. Notably, low response rates are the key contributing factor for the rapid decline in OS.

Although MM remains an incurable disease, the introduction of new therapies; PIs, IMiDs, and mAbs during the last decade has changed the landscape of MM, leading to improved disease control and prolonged survival with an increasing proportion of long-term survivors. Despite these therapeutic advances, nearly all patients with MM will eventually experience relapse and become refractory to available therapies with only two thirds of diagnosed patients remaining alive at five years [3, 4] (see further section 5.2.2 in prognosis within RRMM).

5.1.2 Epidemiology

The prevalence and incidence of MM in Denmark from 2016-2020 are presented in Table 2. In 2020 there were 634 patients diagnosed with MM of which 56% were males. Based on these data from NORDCAN for MM in Denmark, 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 [15-20]. 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 2. Incidence and prevalence of MM in Denmark in 2016 - 2020

Year	2016	2017	2018	2019	2020	Source
Incidence in Denmark	509	538	550	613	634	[21]
Prevalence in Denmark	2,467	2,668	2,853	3,113	34,08	[22]

To estimate the number of patients who would be eligible for the treatment with teclistamab, 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 lines of therapy and are assumed to have received a PI, IMiD, and anti-CD38 mAb [23]. Of the eligible patients, 15% (11 patients) are expected to receive teclistamab the first year on the market, in 2023. Thereafter, a market share is expected to be 25%, 30% and 40% in 2024, 2025 and 2026, respectively (see Table 3).

Table 3. Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	11	18	21	28	28

Sources: Janssen internal assumption.

5.1.3 Patient populations relevant for this application

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 teclistamab and the MajesTEC-1 trial population. This will position

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teclistamab as a fourth- or subsequent-line treatment. The baseline characteristics used in the cost-effectiveness analysis was based on the "all treated population" of the MajesTEC-1 (Phase 1+2 Cohort A, n=165) presented in Table 4. Patients enrolled in MajesTEC-1 had a mean age of 64 years.

Table 4. Baseline characteristics: MajesTEC-1

Characteristic	Value
Age, mean (SD)	63.9 (9.6)
Proportion female	41.8%
Body weight, mean (SD)	75.0 (16.7)
Body surface area, mean (SD)	1.83 (0.24)

Abbreviations: SD, Standard deviation.
Source: Janssen [28].

Subgroup analyses demonstrated that the response to teclistamab was generally consistent across most clinically relevant subgroups such as age, number of prior lines of treatment, refractoriness to the prior therapy, prior hematopoietic stem cell transplantation, cytogenetic risk at baseline, and baseline BCMA expression [24, 25]. 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.

5.2 Current treatment options and choice of comparator(s)

5.2.1 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[26]. 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 [18, 27]. There is a growing body of evidence supporting the goal of reaching deep response, to maximize PFS and OS [24, 28, 29]. As highlighted in the most recent European guidelines [30] MRD negativity in patients who have achieved CR consistently correlates with prolonged PFS and OS in both newly diagnosed and RRMM patients [30].

In Denmark, evidence-based treatment guidelines for MM are provided by DMC and The Danish Myeloma Study Group (DMSG) [26, 31]. The most recent treatment guidelines for MM from DMC, are valid from 1st of July 2022. 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 [31].

Recommended treatment regimens per line of therapy are as follows [31]:

- In second line treatment (first relapse):
  - Patients responsive to lenalidomide (70% of patients): 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).
  - Patient refractory to lenalidomide (70% of patients): daratumumab plus bortezomib and dexamethasone (DVd).
  - Other regimens can be considered, such as pomalidomide plus bortezomib plus dexamethasone or carfilzomib plus dexamethasone.

- 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), pomalidomide plus bortezomib and dexamethasone (PVd) and pomalidomide plus cyclophosphamide and

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dexamethasone (PCd) OR carfilzomib-containing regimens: carfilzomib plus dexamethasone (Kd) and carfilzomib plus lenalidomide and dexamethasone (KRd)
    - Daratumumab may also be considered.

- In fourth line treatment (third relapse or higher) - Treatment selection should take into account refractoriness, toxicity, comorbidity and patient preference:
    - 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)

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.

5.2.2 Prognoses

5.2.2.1 Staging systems and assessment of response to therapy

Clinical outcomes for patients with MM depend on several factors, including intrinsic tumor cell characteristics (cytogenetic abnormalities), tumor burden (stage), patient characteristics (age, comorbidities, frailty) and response to therapy [32, 33]. Both the international staging system (ISS) and the revised ISS (R-ISS) have shown to be strong disease-based prognostic factors for survival in MM. Table 5 includes the five-year survival by R-ISS stage [34, 35]. The R-ISS is currently used primarily for risk stratification of patients in clinical trials and is now considered a standard risk stratification model for patients with NDMM [36].

Table 5. Criteria for staging in MM ISS and R-ISS

Stage	International Staging System (ISS)	Revised International Staging System (R-ISS)	Five-year survival by R-ISS stage
I	Sβ2M < 3.5 mg/L; serum albumin ≥ 3.5 g/dL	Sβ2M < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard-risk chromosomal abnormalities (CA) by FISH Normal LDH	82%
II	Sβ2M < 3.5 mg/L; serum albumin < 3.5 g/dL OR β2M 3.5 to 5.5 mg/L, irrespective of serum albumin	Not R-ISS stage I or III	62%
III	Sβ2M > 5.5 mg/L	Sβ2M ≥ 5.5 mg/L and either High-risk CA by FISH or High LDH	40

Note: VALUES (β2M = Serum β2 microglobulin; ALB = serum albumin.
Source: [34, 35, 37].

In addition to R-ISS as prognostic marker, the therapeutic advantage of MRD assessment has become essential to enhance the evaluation of treatment efficacy and a measurement of disease burden. It is currently well established that there is an association between depth of response and prolonged survival in MM [38, 39]. Definitions of treatment response and disease progression were developed by the IMWG in 2006 and became widely used in clinical practice and clinical trials [40]. The initial 2006 IMWG response criteria included definitions for complete response (CR), very good partial response (VGPR), and partial response (PR). These criteria were subsequently updated in 2014 and 2016 to reflect the greater depth of response that can be achieved with current therapies, including stringent complete response (sCR) and minimal residual disease (MRD) negative status among patients who achieve CR/sCR.

Figure 2 provides a summary of the depths of response to treatment as measured by the total number of remaining malignant MM cells [41]. As observed in other hematologic malignancies, a strong association exists between the depth of response and other key clinical outcomes in MM and RRMM. That is, a greater depth of response is associated with improved survival outcomes and treatment-free intervals. For example, a retrospective analysis of real-world patients with RRMM (N = 139) showed that patients who achieved CR, sCR, or VGPR had a longer median OS than those who

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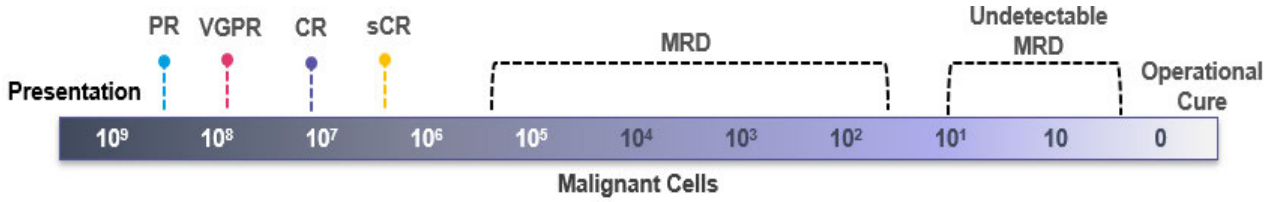
had PR, stable disease (SD), or progressive disease (PD) [42]. Furthermore, the median time to next treatment was longer among patients who experienced a sCR/CR than those with a minimal response or SD. Despite this correlation, nearly all patients eventually experience disease relapse despite achieving deep treatment responses with modern therapeutic agents, reflecting an undetected, persistent disease [40].

Figure 2. Depth of response and their associated levels of malignant cells in MM



Abbreviations: CR = complete response; MRD = minimal residual disease; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.
Source: adapted from Paiva, van Dongen [37]Paiva, van Dongen [36]Paiva, van Dongen [37]Paiva, van Dongen [41].

To account for discrepancies in depth of treatment response and relapse rates in MM, the IMWG incorporated MRD status as part of the updated response criteria [40]. Defined as the number of myeloma cells that remain in the bone marrow after a clinical response to treatment, MRD has been proposed as a key link between initial response and subsequent long-term outcomes, given that residual myeloma cells may lead to disease progression and relapse [43]. Once a CR is suspected or confirmed, the IMWG proposes that MRD be tested throughout the disease course [40]. The Danish treatment guidelines recognize that monitoring of MRD may play a greater role in treatment choice when more evidence is generated on this topic [31]. The prognostic value of MRD in newly diagnosed (ND)MM and in RRMM has been explored in multiple studies and has shown that MRD negativity may predict long-term outcomes and is a superior prognostic factor for both PFS and OS [44-47].

5.2.2.2 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 [3, 4]. Approximately 4% to 12% of MM patients have been estimated to be triple class exposed [5-7]. There are limited data on triple class exposed RRMM, although the existing data point towards a particularly poor prognosis [8, 9], and a high unmet need for effective therapies [10, 11]. As MM progresses, each subsequent line of therapy is associated with shorter PFS and a decreased rate, depth, and durability of response [15-20].

With conventional therapies, mOS ranges from only 8.2 months to 15.7 months [5, 12-14]. Only a few studies have evaluated long-term survival outcomes in this population. Notably, low response rates are the key contributing factor for the rapid decline in OS. Notably, low response rates are the key contributing factor for the rapid decline in OS. For example, among the 12.5% of patients with very good partial response (VGPR) or better in 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 [14].

Studies of HRQoL indicate that patients with RRMM have worse HRQoL than individuals in the general population, and those with other cancer types [27, 48, 49]. 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) [50-53].

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 [54].

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.

5.3 Choice of comparator(s)

The Danish treatment guidelines lists a number of different treatment alternatives for patients in the fourth treatment line. Therefore, a survey in which Danish physicians were interviewed about their treatment patterns in different treatment lines were utilized. According to the survey, patients in the fourth treatment line receive a vast number of different treatments. A heterogenous treatment pattern for fourth line patients is in line with findings from RWE studies carried out in Europe as well as US [55-58].

Taking into account the survey of Danish physician's, the RWE studies, as well as the treatment guidelines (presented in section 5.2.1), it was determined that a mix of currently available SoC is the most relevant comparator. The mix of currently available SoC regimens is henceforth called physician's choice.

Because MajesTEC-1 is a single-arm trial, an external data source is needed to estimate the efficacy of physician's choice. Janssen has identified three potential data sources for comparative effect: The daratumumab trials (POLLUX, CASTOR, EQUULEUS, and APOLLO), Flatiron and the LocoMMotion trial (NCT04035226) [55-58].

LocoMMotion was determined the most relevant source, due to it being a prospective trial (a non-interventional study of real-life SoC) with similar inclusion and exclusion criteria as MajesTEC-1 (see Table 59 and Table 60 for full inclusion and exclusion criteria)) [56, 57] (See further section 7.5 for results from adjusted comparison of teclistamab and physician's choice from LocoMMotion).

The composition is presented in **Error! Not a valid bookmark self-reference.**, and is in line with the DMC guidelines for fourth line treatment in MM (see further Section 5.2.1) [59, 60]. For a list of the regimens received in more than four patients, in LocoMMotion, see further section 18.1.5, Table 70.

Table 6. Physician's choice relevant for Denmark

Physician's choice regimen		Frequency assumed in Danish practice	Source
Kd	Carfilzomib-dexamethasone	21%	[59]
VCd	Bortezomib-cyclophosphamide-dexamethasone	18.9%	[59, 60]
PCd	Pomalidomide-cyclophosphamide-dexamethasone	13%	[59]
Pd	Pomalidomide-dexamethasone	13%	[59]
ERd	Elotuzumab-lenalidomide-dexamethasone	8%	[59]
IRd	Ixazomib-lenalidomide-dexamethasone	8%	[59]
KRd	Carfilzomib-lenalidomide-dexamethasone	4%	[59]
D	Daratumumab	4%	[59]
DVd	Daratumumab-bortezomib-dexamethasone	4%	[59]
Vd	Bortezomib-dexamethasone	4%	[59]
Venetoclax	Venetoclax	2.1%	[59, 60]

Abbreviations: D= Daratumumab; DVd= Daratumumab plus bortezomib plus dexamethasone; ERd= Elotuzumab plus lenalidomide plus dexamethasone; IRd= Ixazomib plus lenalidomide plus dexamethasone; Kd=Carfilzomib plus dexamethasone; KRd= Carfilzomib plus lenalidomide plus dexamethasone; Pd=Pomalidomide plus dexamethasone; PCd=Pomalidomide plus cyclophosphamide plus dexamethasone; Vd= Bortezomib plus dexamethasone; VCd= Bortezomib plus cyclophosphamide plus dexamethasone.

5.3.1 Description of the comparator(s)

See Table 7 for an overview of the regimens included as physician's choice. Also see Table 29.

Table 7. Summary of the combinations included as physician's choice

Regimen	Generic names	ATC code	MoA	Form	Admin	Dosing	Posology	Source
Kd	Carfilzomib	L01XG02	PI	Powder	IV	20/56 mg/m^2	Cycle 1: Start dose of 20 mg/m2 (Days 1 and 2) and increase to 56 mg/m2 (Days 8, 9, 15 and 16) in a 28-day cycle. Cycle 2+: administer 56 mg/m2 on Days 1, 2, 8, 9, 15, and 16	[61, 62]

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	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	20 mg	Days 1, 2, 8, 9, 15, 16, 22, and 23 in a 28-day cycle	
VCd	Bortezomib	L01XG01	PI	Powder	SC	1.3 mg/m^2	Days 1, 8, 15, and 22 in a 5-week cycle	[63]
	Cyclophosphamide	L01AA01	Alkylating agent	Powder	IV	1000 mg/m^2	Days 1 in a 28-day cycle	
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	20 mg	Days 1, 2, 8, 9, 15, 16, 22 and 23 in a 5-week cycle	
PCd	Pomalidomide	L04AX06	IMiD	Capsule	Oral	4 mg	Days 1 through 21, followed by one week break (28-day cycle)	[63, 64]
	Cyclophosphamide	L01AA01	Alkylating agent	Tablet	Oral	500 mg	Days 1, 8, and 15 in a 28-day cycle	
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	40 mg	Days 1, 8, 15, and 22 in a 28-day cycle	
Pd	Pomalidomide	L04AX06	IMiD	Capsule	Oral	4 mg	Days 1 through 21, followed by one week break (28-day cycle)	[61, 64]
	Dexamethasone	H02AB02	Glucocorticoid	Tablet	Oral	40 mg	Day 1, 8, 15, 22 in a 28-day cycle	
ERd	Elotuzumab	L01FX08	mAB	Powder	IV	10 mg/kg	Cycle 1 and 2: Days 1, 8, 15 and 22 (in a 28-day cycle). Cycle 3+: Days 1 and 15 of every 28-day cycle	[61]
	Lenalidomide	L04AX04	IMiD	Capsule	Oral	25 mg	Days 1-21, followed by 1 week rest period (28-day cycle)	
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	40 mg	Days 1, 8, 15 and 22 in a 28-day cycle.	
IRd	Ixazomib	L01XG03	PI	Capsule	Oral	4 mg	Days 1, 8 and 15 in a 28-day cycle	[61]
	Lenalidomide	L04AX04	IMiD	Capsule	Oral	25 mg	Days 1 through 21 in a 28-day cycle	
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	40 mg	Days 1, 8, 15 and 22 of a 28-day cycle	
KRd	Carfilzomib	L01XG02	PI	Powder	IV	20/27 mg/m^2	Cycle 1: Starting dose of 20 mg/m2 (Days 1 and 2 of first cycle), followed by 27 mg mg/m2 on Days 8, 9, 15 and 16 in a 28-day cycle. Cycles 2-12: 27 mg/m2 on Days 1, 2, 8, 9, 15 and 16 in a 28-day cycle. Cycles 13-18: 27 mg/m2 on Days 1, 2, 15 and 16 in a 28-day cycle	[61, 62]
	Lenalidomide	L04AX04	IMiD	Capsule	Oral	25 mg	Days 1 through 21 in a 28-day cycle	
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	40 mg	Days 1, 8, 16 and 22 in a 28-day cycle	
D	Daratumumab	L01FC01	mAB	Powder	SC	1,800 mg	Weekly for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter	[61, 65]
DVd	Daratumumab	L01FC01	mAB	Powder	SC	1,800 mg	Weekly for 9 weeks, then once every 3 weeks for 15 weeks, and every 4 weeks thereafter (21-day cycle)	[61, 65]
	Bortezomib	L01XG01	PI	Powder	SC	1.3 mg/m^2	Days 1, 4, 8 and 11 in a 21-day cycle	

	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	20	Days 1, 2, 4, 5, 8, 9, 11 and 12 (21-day cycle)	
Vd	Bortezomib	L01XG01	PI	Powder	SC	1.3 mg/m^2	Days 1, 4, 8, and 11 in a 21-day cycle	[63]
	Dexamethasone	H02AB02	Gluco-corticoid	Tablet	Oral	20 mg	Days 1, 2, 4, 5, 8, 9, 11, and 12 in a 21-day cycle	
Venetoclax	Venetoclax	L01XX52	Selective inhibitor	Tablet	Oral	1,200 mg	Days 1 through 21, followed by one week break (28-day cycle)	[66]

Abbreviations: D= Daratumumab; DVd= Daratumumab plus bortezomib plus dexamethasone; ERd= Elotuzumab plus lenalidomide plus dexamethasone; IRd= Ixazomib plus lenalidomide plus dexamethasone; Kd=Carfilzomib plus dexamethasone; KRd= Carfilzomib plus lenalidomide plus dexamethasone; Pd=Pomalidomide plus dexamethasone; PCd=Pomalidomide plus cyclophosphamide plus dexamethasone; Vd= Bortezomib plus dexamethasone; VCd= Bortezomib plus cyclophosphamide plus dexamethasone.
Notes: 1) Treatment duration for these regimens is until disease progression or unacceptable toxicity occurs. 2) A market dynamics survey and a Danish clinical expert confirmed the relevance of these regimens in Danish clinical practice [59, 60].

As previously mentioned the Danish guidelines list a number of different treatment options in 4th line, and not all of the treatments listed above are relevant in Danish clinical practice. The Danish Medicines Council have assessed Carvykti which has the same indication as Tecvayli (unpublished). In that assessment they conclude that treatment in 4th line will consist of combinations including carfilzomib or pomalidomide, and approximately 50% of the LocoMMotion cohort receive one of these combinations. They also accept LocoMMotion as the comparator arm and conclude that the uncertainty added by the difference in treatments is of minor importance given that all LocoMMotion patients had received a PI, IMID and anti-CD38 antibody which is also the case for a Danish 4th line patient.

5.4 The intervention

Teclistamab is an off-the-shelf, T-cell redirecting bispecific antibody. It is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including a PI, IMiD, and anti-CD38 mAb and have demonstrated disease progression on the last therapy [67].

Mode of action: T-cell redirecting bispecific antibody that targets both B-cell maturation antigen (BCMA), a marker found on multiple myeloma cells, and cluster of differentiation (CD) 3, on T-cells [67].

Pharmacotherapeutic class (ATC code): Not assigned (Oncology)

Pharmaceutical form: Teclistamab is available as a solution for injection. The 3 mL vial contains 30 mg of teclistamab (10 mg/mL) and the 1.7 mL vial contains 153 mg of teclistamab (90 mg/mL) (Table 8).

Table 8. Different teclistamab strengths

	Packaging type	Pack size	Strength
Teclistamab (priming dose only)	Solution for injection (3 ml vial)	1	10 mg/ml
Teclistamab	Solution for injection (1.7 ml vial)	1	90 mg/ml

Form of administration: Teclistamab should be administered by subcutaneous (SC) injection by a healthcare professional [67].

Dosing: The recommended dosage of teclistamab is 1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule (Table 9). A less frequent (biweekly) administration of teclistamab was approved by EMA on 16 Aug, 2023 with the following statement: "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". The dosing has already been adopted/exceeded by Danish clinicians treating patients in the early access program. This program included 20+ patients in 2022 and a substantial proportion of these patients are still on treatment. Clinicians have decided to increase the dosing interval for these patients with ongoing response to biweekly schedules.

In MajesTEC-1 dosing were based on depth and duration of response. Subjects of MajesTEC-1 could switch from weekly to Q2W and subsequently to Q4W. The treatment dose for Q2W or Q4W was the same as the weekly dosing. Overall, 63 subjects (38.2%) switched from weekly to Q2W dosing with a median time to Q2W dosing at 11.3 months (range: 3.2 to 29.5). Also see section 8.5.1.1.

Teclistamab should be continued until disease progression or unacceptable toxicity [1]. Failure to follow the recommended doses or dosing schedule for initiation of therapy or re-initiation of therapy after dose delays may result in increased frequency and severity of adverse events (AEs) related to mechanism of action, particularly cytokine release syndrome (CRS) [1].

Table 9. Teclistamab step-up dosing schedule

	Teclistamab dose[a]	Dose schedule
Step-up dose 1	0.06 mg/kg	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

[a]Dose is based on actual body weight and should be administered subcutaneously. Source: [67].

Treatment plan: Prior to starting treatment with teclistamab, anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation per local institutional guidelines [1]. Pre-medications are required one to three hours before each dose of the teclistamab step-up dosing schedule to reduce the risk of CRS [1]:

- Corticosteroid (oral or intravenous dexamethasone, 16 mg)
- Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)

Administration of pre-treatment medications may be required for subsequent doses after dose delays.

Treatment duration / Criteria for end of treatment: Teclistamab is administered until disease progression or unacceptable toxicity [1].

Packaging type, size and strength: Patients are treated with one of the teclistamab strengths presented in Table 10.

Table 10. Packaging type, size and strength

	Packaging type	Pack size	Strength
Teclistamab (priming dose only)	Solution for injection (3ml vial)	1	10 mg/ml
Teclistamab	Solution for injection (1.7 ml vial)	1	90 mg/ml

Monitoring: 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 teclistamab step-up dosing schedule.

Change to current treatment algorithm:

Figure 3 summarizes the change to current treatment algorithm of RRMM in the Danish treatment landscape and where teclistamab should be used. It is expected that teclistamab 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 [67], which will place teclistamab as an option for fourth or subsequent lines of therapy in MM.

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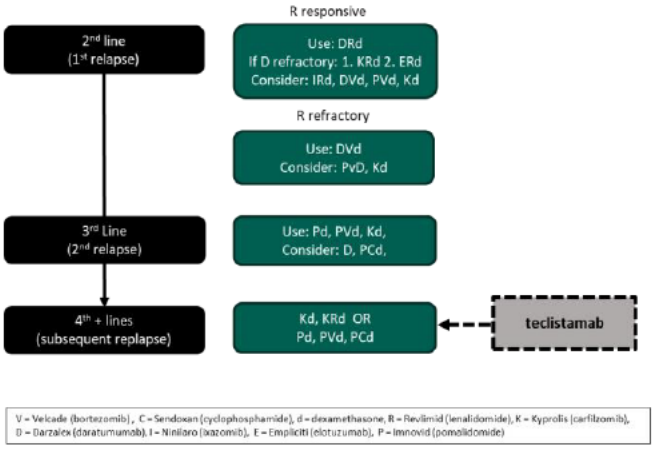
Figure 3. Change to current treatment algorithm



Note: This figure only represents the teclistamab positioning in relation to the current treatment guidelines from DMC. 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.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The pivotal study investigating teclistamab is the MajesTEC-1 study (NCT03145181 and NCT04557098) [68, 69]. Hence, MajesTEC-1 provides the basis for the efficacy and safety evidence in this assessment. The clinical development program for teclistamab in RRMM includes five additional ongoing clinical trials, summarized in Table 11.

The study LocoMMotion (MMY4001)[70, 71] provides the basis for the efficacy and safety evidence for physician's choice (comparator) in this assessment. This study was considered the most relevant data source for physician's choice because of its similar inclusion criteria to the MajesTEC-1 trial and its prospective design (see further section 7.5 and Appendix F Comparative analysis of efficacy and safety).

A systematic literature review (SLR) was not the basis for choice of comparative effectiveness s in this analysis, as such the most relevant documentation for efficacy and safety (intervention and comparator) were determined to be the above-mentioned studies. However, Janssen has carried out an SLR and more information relating to that is found in Appendix A (including the full SLR).

6.2 List of relevant studies

6.2.1 Relevant studies included in the assessment

Table 11 presents a summary of the relevant studies included in this assessment. For detailed information about included studies, see Appendix B.

Table 11. Relevant studies included in the assessment

Title, author, journal and year	Trial name	NCT number	Dates of study (start and expected completion date)	Reference
A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA×CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory	MajesTEC-1	NCT03145181 (phase 1)	Ongoing Study start date: May 2017 Estimated study completion date: Not applicable, study is ongoing	[68, 69]

Title, author, journal and year	Trial name	NCT number	Dates of study (start and expected completion date)	Reference
Multiple Myeloma. Janssen data on file 2023 Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Usmani et al. Lancet. 2021		NCT04557098 (phase 2)	Ongoing Study start date: September 2020 Estimated study completion date: Not applicable, study is ongoing	[68, 69]
Study JNJ-68284528 LocoMMotion CSR. Final, All Outputs - Updated 11MAY2023, Cutoff 27OCT2022, Final Data. Janssen data on file 2023 A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving≥ 3 prior lines of therapy. Mateos et al. Wolters Kluwer Health. 2021	LocoMMotion	NCT04035226	Ongoing Study start date: August 2019 Estimated study completion date: October 2022	[70, 71]

6.2.2 Ongoing studies

There are several other ongoing teclistamab studies and, more information is provided in Appendix B Main characteristics of included studies, section 14.1.

7. Efficacy and safety

7.1 MajesTEC-1

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, inclusion and exclusion criteria as well as study end points are described in detail in Appendix B. Demographics and baseline characteristics for the All Treated Analysis Set (n=165) are shown in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.2 LocoMMotion

The ongoing study, LocoMMotion (MMY4001) provides the basis for the efficacy and safety evidence for physician's choice (comparator) in this assessment. LocoMMotion was considered the most relevant data source for the comparative efficacy (see further section 7.5.3 for the results from the adjusted treatment comparison for MajesTEC-1 and LocoMMotion). The study consists of the all treated analysis set, 248 participants enrolled between August 2019 and October 2020 at 76 sites across nine European countries and the US [56, 57]. The clinical cut-off date for the present analysis was October, 2022 and the median follow up duration was 26.41 months. For further details on LocoMMotion study design, inclusion and exclusion criteria as well as study end points are described in detail in Appendix B. Demographics and baseline characteristics for the all enrolled i.e. all treated (n=248) in LocoMMotion are shown in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety (LocoMMotion and MajesTEC-1).

7.3 Efficacy and safety – MajesTEC-1 results

7.3.1 Progression free survival

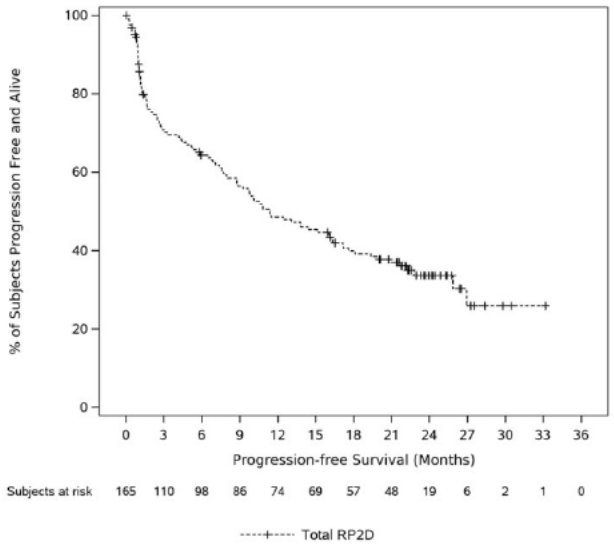
With a median follow-up of 22.8 months in the All Treated Analysis Set in MajesTEC-1, median PFS per IRC was 11.3 months (95% CI: 8.8 to 16.4), (Table 12). Kaplan-Meier plots for PFS by IRC assessment are provided in Figure 4. One hundred and two subjects (61.8%) had a PFS event by IRC assessment: 76 subjects had progressive disease and 26 subjects died without progressive disease.

Table 12. Progression-Free Survival based on Independent Review Committee Assessment; All Treated Analysis Set

PFS Results	Total n = 165
Number of events (%)	102 (61.8%)
Number of censored	63 (38.2%)
Kaplan–Meier estimate (months)	
25% percentile (95% CI)	2.1 (1.2, 4.3)
Median (95% CI)	11.3 (8.8, 16.4)
75% percentile (95% CI)	NE (25.9, NE)
6-month progression-free survival rate % (95% CI)	64.4 (56.4, 71.3)
9-month progression-free survival rate % (95% CI)	56.5 (48.3, 63.9)
12-month progression-free survival rate % (95% CI)	48.6 (40.5, 56.2)
18-month progression-free survival rate % (95% CI)	39.9 (32.1, 47.5)
24-month progression-free survival rate % (95% CI)	33.7 (25.9, 41.6)

Abbreviations: CI = confidence interval; NE = not estimable, PFS = progression-free survival; IRC = independent review committee; IMWG = international myeloma working group Note: Progressive disease was assessed by IRC, based on IMWG consensus criteria (2016). Sources: [69]

Figure 4. Kaplan-Meier Plot for Progression-Free Survival based on Independent Review Committee Assessment; All Treated Analysis Set



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). Sources: [69]

7.3.2 Overall survival

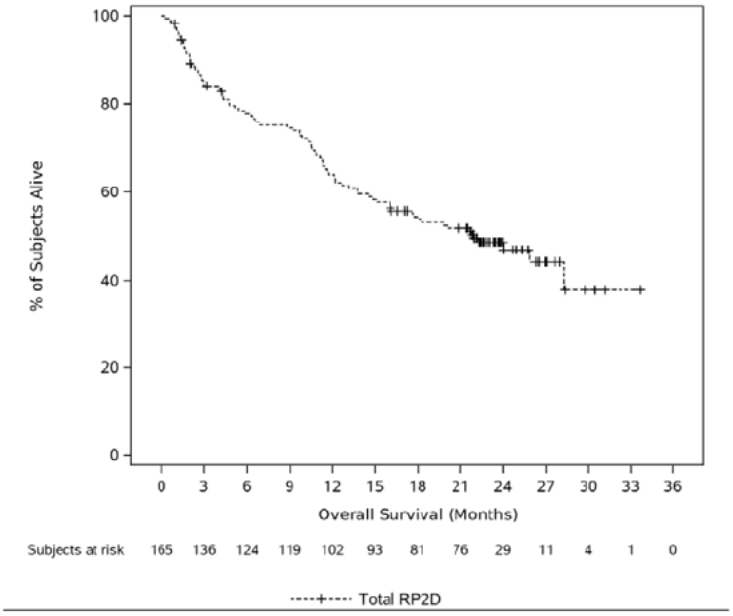
With a median follow-up of 22.8 months in the All Treated Analysis Set, median OS was 21.9 months (95% CI: 15.1 to NE) (Table 9). A Kaplan-Meier plot for OS is provided in Figure 5.

Table 13. Overall survival; All Treated Analysis Set

OS Results	Total n = 165
Number of events (%)	84 (50.9%)
Number of censored (%)	81 (49.1%)
Kaplan-Meier estimate (months)	
25% percentile (95% CI)	8.8 (4.2, 10.8)
Median (95% CI)	21.9 (15.1, NE)
75% percentile (95% CI)	NE (28.3, NE)
6-month overall survival rate % (95% CI)	77.8 (70.6, 83.4)
9-month overall survival rate % (95% CI)	74.7 (67.2, 80.7)
12-month overall survival rate % (95% CI)	64.0 (56.0, 70.9)
18-month overall survival rate % (95% CI)	54.5 (46.4, 61.8)
24-month overall survival rate % (95% CI)	48.7 (40.5, 56.3)

Abbreviations: CI = confidence interval; NE = not estimable; OS = overall survival.
Source: [69]

Figure 5. Kaplan-Meier Plot for Overall Survival; All Treated Analysis Set



Abbreviations: RP2D = recommended Phase 2 dose.
Source: [69]

7.3.3 Overall response rate

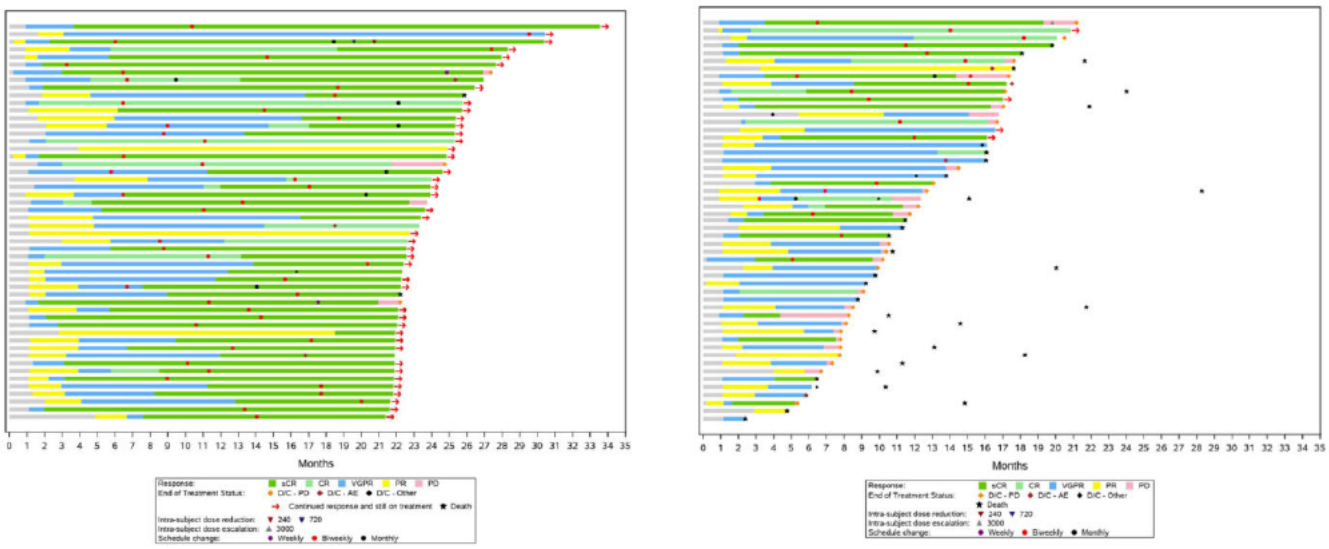
ORR (rate of PR or better), as assessed by the IRC based on IMWG 2016 criteria, in the All Treated Analysis Set (N=165) was 63.0% (95% CI: 55.2 to 70.4), with similar ORR in each phase (Table 14). Responses are illustrated for each responder in Figure 6. Most responses occurred early (by the start of Cycle 2) and deepened over time. Sixty-three of 104 responders switched from weekly to Q2W dosing during the study. Forty-one subjects remained in response and were still on treatment at the time of the CCO, with a range of 1 to 25 months of follow-up after the initial dose schedule change (Figure 6). A best response of VGPR or better as assessed by the IRC was reported for 59.4% (95% CI: 51.5 to 67.0) of subjects. A best response of CR or better was reported for 45.5% (95% CI: 37.7 to 53.4) of subjects. A best response of sCR was reported for 37.6% (95% CI: 30.2 to 45.4) of subjects.

Table 14. Overall best confirmed response rates for teclistamab in MajesTEC-1

Response n (%) (95% CI)	All Treated Analysis Set n = 165
Response category	**n=165**
Stringent complete response (sCR)	62 (37.6%) (30.2%, 45.4%)
Complete response (CR)	13 (7.9%) (4.3%, 13.1%)
Very good partial response (VGPR)	23 (13.9%) (9.0%, 20.2%)
Partial response (PR)	6 (3.6%) (1.3%, 7.7%)
Minimal response (MR)	2 (1.2%) (0.1%, 4.3%)
Stable disease (SD)	28 (17.0%) (11.6%, 23.6%)
Progressive disease	23 (13.9%) (9.0%, 20.2%)
Not evaluable	8 (4.8%) (2.1%, 9.3%)
Overall response (sCR + CR + VGPR + PR)	**104 (63.0%) (55.2%, 70.4%)**
VGPR or better (sCR + CR + VGPR)	98 (59.4%) (51.5%, 67.0%)
CR or better (sCR + CR)	75 (45.5%) (37.7%, 53.4%)

Abbreviations: CI = confidence interval; NE = not estimable; IRC = independent review committee; IMWG = international myeloma working group
Note: Response was assessed by IRC, based on IMWG consensus criteria (2016). Percentages calculated with the number of subjects in the all treated analysis set as denominator. Note: Exact 95% confidence intervals are provided.
Sources: [69]

Figure 6. Response and Follow-up Based on Independent Review Committee Assessment; Responders in the All Treated Analysis Set



Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; sCR = stringent complete response; VGPR = very good partial response; IRC = independent review committee; IMWG = international myeloma working group; D/C = discontinued.

Note: Response was assessed by IRC, based on IMWG consensus criteria (2016).

7.3.4 Time to response

The median time to first response (PR or better), best response, VGPR or better, and CR or better is provided in Table 15. Median time to best response was 4.0 months (range: 1.1 to 18.7).

Table 15. Descriptive Summaries for Time to Response based on Independent Review Committee Assessment; Responders in the All Treated Analysis Set (n = 165)

Responders in the All Treated Analysis Set	n = 104
Time to first response (months)[a]	N=104
Mean (SD)	1.45 (0.885)
Median	1.18
Range	(0.2; 5.5)
Time to best response (months)[a]	N=104
Mean (SD)	6.10 (4.718)
Median	3.96
Range	(1.1; 18.7)
Time to VGPR or better (months)	N=98
Mean (SD)	2.91 (2.480)
Median	2.23
Range	(0.2; 18.5)
Time to CR or better (months)	N=75
Mean (SD)	6.47 (4.808)
Median	4.63
Range	(1.6; 18.5)

Abbreviations: IRC = independent review committee; VGPR = very good partial response; CR =complete response; PR = partial response; IMWG = international myeloma working group

Note: [a] Response PR or better. Response was assessed by IRC, based on IMWG consensus criteria (2016).

Source: [69]

7.3.5 Duration of response

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

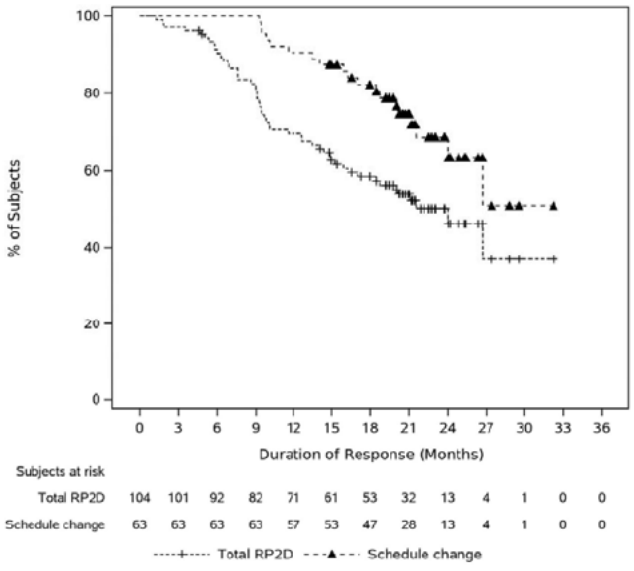
to any cause. Among responders, median DOR at the CCO was 21.6 months (95% CI: 16.2 to NE) (Table 16). In the 63 subjects who switched to Q2W dosing, median DOR was not reached. The probability of responders remaining in response at 24 months was 49.9% (95% CI: 39.0 to 59.9). Kaplan-Meier curves for DOR for subjects in the All Treated Analysis Set and for responders with a schedule change are provided in Figure 7.

Table 16. Duration of Response based on Independent Review Committee Assessment (Events Defined as Disease Progression or Death due to Any Cause); Responders in the All Treated Analysis Set (n=165)

Responders in the All Treated Analysis Set	n = 104
Duration of response (months)[a]	
Number of events (%)	50 (48.1%)
Number of censored (%)	54 (51.9%)
Kaplan-Meier estimate (months)	
25% percentile (95% CI)	9.5 (7.6, 13.5)
Median (95% CI)	21.6 (16.2, NE)
75% percentile (95% CI)	NE (26.7, NE)
Range	(1, 32+)
6-month event-free rate % (95% CI)	90.3 (82.7, 94.6)
9-month event-free rate % (95% CI)	80.5 (71.4, 86.9)
12-month event-free rate % (95% CI)	69.7 (59.8, 77.6)
18-month event-free rate % (95% CI)	58.5 (48.3, 67.4)
24-month event-free rate % (95% CI)	49.9 (39.0, 59.9)

Note: [a]Duration of response is calculated as the number of months from first documented response to progression, death due to any cause, or date of censoring. Number of events refers to number of responders (PR or better) who developed disease progression or died due to any cause. Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
Abbreviations: CI = confidence interval; NE = not estimable; + = censored observation; RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group; PR = partial response
Source: [69]

Figure 7. Kaplan-Meier Plot for Duration of Response Based on Independent Review Committee Assessment (Events Defined as Disease Progression or Death due to Any Cause); All Responders and Responders with Schedule Change in the All Treated Analysis Set



Abbreviations: RP2D = recommended Phase 2 dose; IRC = independent review committee; IMWG = international myeloma working group
Note: Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
Source: [69]

7.3.6 Switching to Q2W Dosing

Subjects of MajesTEC-1 could switch from weekly to Q2W and subsequently to Q4W. The treatment dose for Q2W or Q4W dosing in the All Treated Set was the same as the applicable subject's weekly dosing. Overall, 63 subjects (38.2%) in the All Treated Analysis Set switched from weekly to Q2W dosing, including 54 subjects who met the response criteria stipulated in the protocol per investigator assessment [69]. Investigator response was used to guide the dosing frequency, as this could be obtained in real-time. Of the 63 subjects who switched from weekly to Q2W dosing, 54 subjects were in CR or better and 9 subjects were in PR or VGPR per IRC. Median time to Q2W dosing in the All Treated Analysis Set was 11.3 months (range: 3.2 to 29.5). Median duration of follow-up after schedule change to Q2W dosing was 12.6 months (range: 1.0 to 24.7). Overall, 47 subjects remain on treatment and the majority of these (n=42 [89.4%]) are receiving less frequent dosing (i.e., Q2W and subsequently Q4W dosing, if applicable), 9 subjects had switched from Q2W to Q4W dosing [69]. Dose switching according to the following statement *"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"* was approved by EMA August the 16th 2023. Additionally, the EMA approved dosing schedule has already been adopted/exceeded by Danish clinicians treating patients in the early access program. This program included 20+ patients in 2022 and a substantial proportion of these patients are still on treatment. Clinicians have decided to increase the dosing interval for these patients with ongoing response to biweekly schedules.

7.3.7 Safety

The safety profile of teclistamab is consistent with the mechanism of action with respect to T-cell activation and targeting of B cells as demonstrated in MajesTEC-1. At least 1 any grade TEAE was reported for all 165 subjects (100.0%) in the All Treated Analysis Set (Table 17). Serious TEAE(s) were reported for 113 subjects (68.5%). Maximum Grade 3 TEAE(s) were reported for 28 subjects (17.0%) and maximum Grade 4 TEAE(s) were reported for 94 subjects (57.0%). Thirty-four subjects (20.6%) experienced a maximum Grade 5 TEAE; 25 of these subjects had cause of death reported as AE (including 18 subjects with maximum Grade 5 AE of COVID-19) and 9 had cause of death reported as progressive disease. Seven of the Grade 5 TEAEs were judged by the investigator to be related to teclistamab. Eight subjects (4.8%) experienced a TEAE reported as leading to treatment discontinuation [69].

Table 17. Overall Summary of Treatment-emergent Adverse Events; All Treated Analysis Set

Treatment-emergent Adverse Events	n=165
Any TEAE	165 (100.0%)
Study drug-related[a]	154 (93.3%)
Maximum toxicity grade	
Grade 1	1 (0.6%)
Grade 2	8 (4.8%)
Grade 3	28 (17.0%)
Grade 4	94 (57.0%)
Grade 5	34 (20.6%)
Any serious TEAE	113 (68.5%)
Study drug-related[a]	53 (32.1%)
TEAE leading to discontinuation of study drug[b]	8 (4.8%)
TEAE with outcome death[c]	34 (20.6%)
Death due to COVID-19	18 (10.9%)
COVID-19 TEAEs	48 (29.1%)
COVID-19 serious TEAEs	34 (20.6%)

Abbreviations: TEAE = treatment-emergent adverse event

Note: a TEAEs related to study drug; b Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment; c TEAE with outcome death on the AE. Percentages calculated with the number of subjects in the all treated analysis set as denominator.

Source: [69]

Two events of CRS have been reported since the CCO for the primary analysis for MajesTEC-1, both in the same subject with a prior event of CRS. These events, which were Grade 1 in severity, occurred after a delay in treatment. Note that the total number of subjects who experienced CRS in the pivotal population of MajesTEC-1 (n=119 [72.1%]) includes a subject not reported as having CRS in the primary analysis due to an event being entered in the database after the database lock. No additional events of ICANS were reported since the CCO for the primary analysis for MajesTEC-1. At least 1 Grade 3 or 4 TEAE was reported for 156 subjects (94.5%) in the All Treated Analysis Set and a summary of those

reported in ≥5% of subjects are presented in Table 18. Grade 3 or 4 events were most frequently reported in the SOCs of Blood and Lymphatic System Disorders (144 subjects [87.3%]) and Infection and Infestations (91 subjects [55.2%]), with the following events occurring in ≥10% of subjects in any SOC:

- Neutropenia: 108 subjects (65.5%)
- Anemia: 62 subjects (37.6%)
- Lymphopenia: 57 subjects (34.5%)
- Thrombocytopenia: 37 subjects (22.4%)
- COVID-19: 34 subjects (20.6%)
- Pneumonia: 22 subjects (13.3%).

Table 18. Most Common (≥5% in Total) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set

Grade 3 or 4 Treatment-emergent Adverse Events in ≥5%	n=165
Subjects with 1 or more grade 3 or 4 TEAEs	**156 (94.5%)**
Blood and lymphatic system disorders	144 (87.3%)
Neutropenia	108 (65.5%)
Anemia	62 (37.6%)
Lymphopenia	57 (34.5%)
Thrombocytopenia	37 (22.4%)
Leukopenia	15 (9.1%)
Infections and infestations	91 (55.2%)
COVID-19	34 (20.6%)
Pneumonia	22 (13.3%)
Metabolism and nutrition disorders	44 (26.7%)
Hypophosphatemia	11 (6.7%)
Vascular disorders	16 (9.7%)
Hypertension	10 (6.1%)

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, with the exception of CRS. 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 for CRS by ASTCT is presented in this table, for both Phase 1 and Phase 2. The output includes the diagnosis of CRS; the symptoms of CRS are excluded. 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.
Abbreviations: TEAE = treatment-emergent adverse event; RP2D = recommended Phase 2 dose; CRS = cytokine release syndrome
Source: [69]

Section 7.5.5 present the AEs relevant to the assessment for teclistamab and physician's choice respectively.

7.3.8 Patient reported outcomes

The patient reported outcomes (PRO) measures (EORTC QLQ-C30 and EQ-5D-5L) was administered during site visits to assess the subject's HRQoL after treatment and change from baseline. These measures was administered according to the relevant Time and Events Schedules and was completed by the patient before any clinical tests, procedures, or other consultations. The PRO measures will be provided in the local language. During the follow-up phase, a back-up method for PRO data collection was provided for the patient if the patient did not return to the site for their scheduled visit or if the visit was conducted by home healthcare or tele-health. During the follow-up phase, PRO was collected every 16 weeks (+/-2 weeks) after the initial indication of progressive disease or the end of treatment visit, whichever occurs first. PRO measures was collected after subsequent therapy has been started.

PRO were only assessed for patients enrolled in the phase 2 cohort A of MajesTEC-1 (n=125) and are presented for in Appendix K Patient reported outcomes for the clinical cut-off 4th of January 2023. A significant share of patients using teclistamab reported important improvements/symptom relieve during the first 16 treatment cycles. The baseline compliance rates for all PRO assessments were high (83% and 77% for EORTC QLQ-C30 and EQ-5D-5L, respectively) and remained high (≥63%) throughout the trial (Table 79 and Table 80). The summary for the change from baseline over the cycles in EQ-5D and EQ-5D visual analogue scale (VAS) are presented in Table 81, in which an improvement in scores are seen over the first 16 cycles. Similarly, most patients reported meaningful ≥10-point improvements in MM symptoms from baseline through the first 16 cycles of teclistamab therapy in EORTC-QLQ-C30 scales (Table 82).

7.4 Efficacy and safety – LocoMMotion results

7.4.1 Efficacy

At the time of the analysis (27 October 2022), the median response was measurable in all patients in the all -treated analysis population (n=248 patients). Table 19 gives an overview of the efficacy results for some of the main outcomes in LocoMMotion for the all -treated population. The Kaplan-Meier curves for PFS and OS are presented in

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Figure 8 and Figure 9 respectively. Median PFS was 4.07 months (95% CI: 2.86, 5.39) while the median OS was 13.04 months (95% CI: 8.87, 16.43).

Table 19. Overview of efficacy results for physicians' choice

Outcome	Physician's choice n=248	95% CI
Progression-free survival		
Number of events (%)	171 (69.0%)	
Number of censored (%)	77 (31.0%)	
Kaplan-Meier estimate (months)		
25% quantile	2.04	(1.68, 2.56)
Median	4.63	(3.94, 5.62)
75% quantile	9.92	(8.18, 13.86)
6-month progression-free survival rate %	40.9	(34.1, 47.7)
12-month progression-free survival rate %	21.0	(15.3, 27.3)
18-month progression-free survival rate %	14.0	(9.1, 20.0)
24-month progression-free survival rate %	10.5	(6.1, 16.3)
Overall survival		
Number of events (%)	158 (63.7%)	
Number of censored (%)	90 (36.3%)	
Kaplan-Meier estimate (months)		
25% quantile	5.72	(4.83, 6.44)
Median	13.83	(10.84, 16.99)
75% quantile	30.95	(24.57, NE)
6-month overall survival rate %	73.1	(67.0, 78.2)
12-month overall survival rate %	53.4	(46.7, 59.6)
18-month overall survival rate %	42.5	(35.9, 49.0)
24-month overall survival rate %	33.7	(27.3, 40.2)
Overall response (sCR + CR + VGPR + PR) n (%)	79 (31.9%)	(26.1%, 38.0%)
Stringent complete response (sCR)	0	(NE, NE)
Complete response (CR)	1 (0.4%)	(0.0%, 2.2%)
Very good partial response (VGPR)	32 (12.9%)	(9.0%, 17.7%)
Partial response (PR)	46 (18.5%)	(13.9%, 24.0%)
Minimal response (MR)	14 (5.6%)	(3.1%, 9.3%)
Stable disease (SD)	78 (31.5%)	(25.7%, 37.6%)
Progressed disease (PD)	43 (17.3%)	(12.8%, 22.6%)
Not evaluable (NE)	34 (13.7%)	(9.7%, 18.6%)
Time to response (defined as PR or better)		
Number of events (%)	79 (31.9%)	
Number of censored (%)	169 (68.1%)	
Kaplan-Meier estimate (months)		
25% quantile	2.33	(1.87, 2.79)
Median	5.65	(3.91, 9.53)
75% quantile	25.79	(9.53, NE)

Note: PFS and response was assessed by response review committee (RRC), based on International Myeloma Working Group (IMWG) consensus criteria (2016). Source: [71]

Figure 8. Kaplan-Meier curve for progression-free survival based on Response Review Committee assessment

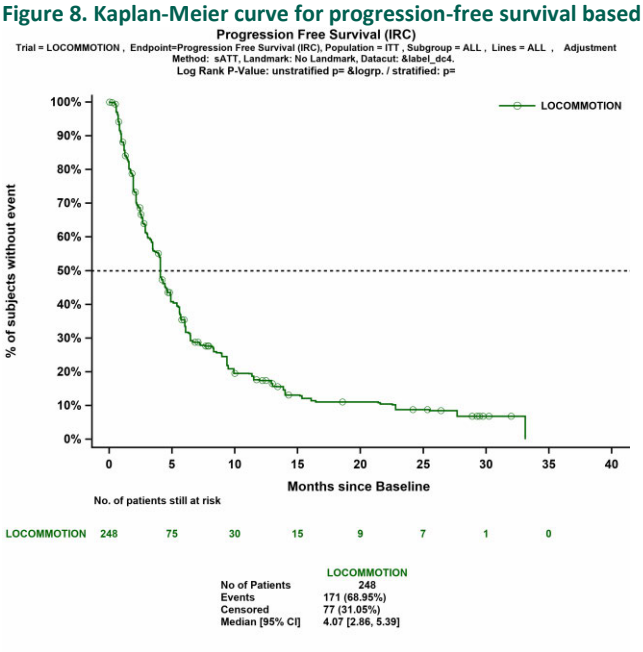
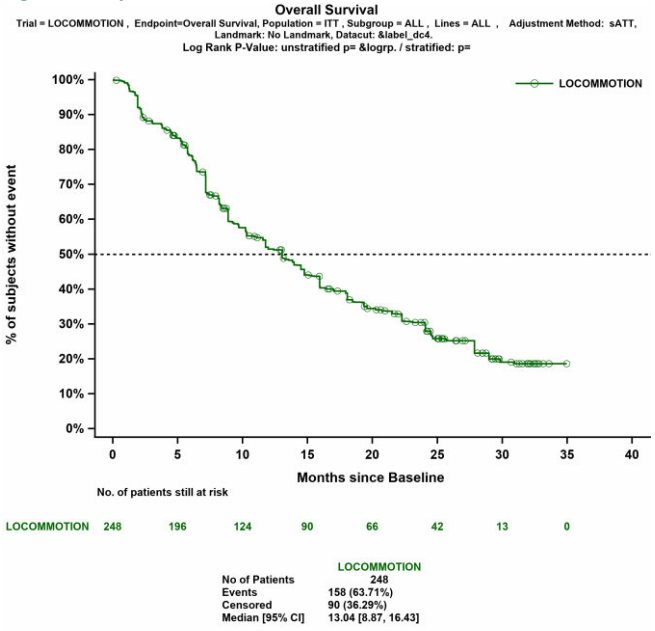


Figure 9. Kaplan-Meier curve for overall survival – LocoMMotion



7.4.2 Safety

A total of 215 participants (86.7%) who received PC treatment experienced at least 1 TEAE. Serious TEAEs were observed in 91 participants (36.7%). A total of 23 participants (9.3%) reported TEAEs that resulted with discontinuation of therapy and a total of 21 participants (8.5%) experienced a TEAE with an outcome of death, and the most frequently reported TEAEs leading to death were infections and infestations (13 participants [5.2%]), including 6 cases of sepsis. At least 1 Grade 3 or 4 TEAE was reported for 144 subjects (58.1%) and a summary of those reported in ≥5% of subjects are presented in Table 20. The most common TEAEs included blood and lymphatic system disorders. The grade 3 and 4 TEAEs in ≥5% of participants (Total and Toxicity Grade of 3 or 4), from the LocoMMotion study are presented in Table 67 in Appendix E [71].

Table 20. Most Common (≥5% in Total) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term

Grade 3 or 4 Treatment-emergent Adverse Events in ≥5%	n=248
Total number of participants with TEAE	144 (58.1%)
MedDRA system organ class/preferred term	
Blood and lymphatic system disorders	101 (40.7%)
Thrombocytopenia	48 (19.4%)
Anemia	27 (10.9%)
Neutropenia	43 (17.3%)
Leukopenia	15 (6.0%)
Lymphopenia	19 (7.7%)
Gastrointestinal disorders	9 (3.6%)
Infections and infestations	20 (8.1 %)

7.4.3 Patient-reported outcomes

Where permitted per local regulations, study physicians obtained HRQoL data from participants in this study. These were collected either during hospital visits or remotely via the phone during the follow-up period until the end-of-study, unless the participant had died, was lost to follow-up, or had withdrawn consent. Questionnaires for PRO measures included EORTC QLQ-C30, EORTC QLQ-IL39 (formerly known as EORTC QLQ-MY20), and EQ-5D-5L

In LocoMMotion, the PROs were assessed for theall treated (n=248). The mean compliance rates for all PRO assessments were high (above 70% for both EORTC QLQ-C30 and EQ-5D-5L) (Table 83 in Appendix K Patient reported outcomes). The changes from baseline from LocoMMotion are presented for EQ-5D-5L and EORTC QLQ-C30 respectively (Table 84 and Table 85) [71].

7.5 Comparative analyses of efficacy and safety

7.5.1 Method of synthesis

Due to the absence of a comparator arm in MajesTEC-1, an external control arm was used to establish the comparative efficacy of teclistamab versus physician's choice. Absolute outcomes of the former were based on MajesTEC-1, while the corresponding information of the latter were based on LocoMMotion [57, 70].

The intention-to-treat (ITT) populations in MajesTEC-1 and LocoMMotion were considered analogous and were compared in the current analyses. The ITT population in MajesTEC-1 included all participants who were treated with teclistamab with the index date defined as the date of first dose. The ITT population in the physician's choice cohort consisted of all participants who satisfied the eligibility criteria outlined, with the index date defined as Day 1 Cycle 1 of the real-life SOC treatment. Using available individual patient-level data for teclistamab (MajesTEC-1) and physician's choice (LocoMMotion), adjusted comparisons were conducted and participants were balanced for prognostic factors. The adjusted comparisons were conducted using inverse probability of treatment weighting (IPTW). Propensity score weighting represents a robust and commonly used technique in comparative efficacy research in the absence of head-to-head clinical trials [72].

The main analyses estimated the average treatment effect on the treated population (ATT), the practical implication being that the adjustments were conducted on the LocoMMotion data (while the MajesTEC-1 data remained unchanged) [73, 74]. Prognostic factors were selected a priori considering both prognostic value and imbalances between trials and were evaluated and ranked by clinical experts [73, 74]. The steps undertaken for identifying and rank-ordering prognostic factors are outlined below.

1. Prior to conducting the analyses, a pool of potential prognostic variables was identified by consulting studies from a literature review conducted to identify clinical outcomes in triple-class exposed RRMM patients, as well as input from clinical experts.

2. Analyses including all available variables with sufficient data were considered as the "Main Analysis".

3. Variables with a high degree of missingness were adjusted for as a sensitivity analysis. These factors were ranked according to availability and level of missingness within the included studies.

The following covariates were adjusted for in the main analyses:

- refractory status
- ISS stage
- time to progression on last regimen
- extramedullary plasmacytomas
- number of prior lines of treatment
- years since MM diagnosis
- average duration of prior lines
- age
- hemoglobin levels
- Lactate dehydrogenase (LDH) levels
- creatinine clearance
- ECOG score
- sex
- type of MM
- prior stem cell transplant

The Main analyses considered the first treatment line initiated after becoming eligible.

7.5.2 Results from head-to-head studies

No head-to-head studies are available for teclistamab. Instead, an adjusted comparison versus SOC (physician's choice) was conducted. Results from MajesTEC-1 and LocoMMotion, separately, were presented above, and the results from the adjusted comparison will follow.

7.5.3 Results from the comparative analysis

In the current set of analyses, comparative efficacy of teclistamab versus PC was estimated on ORR, ≥CR rate, ≥VGPR rate, PFS, DoR, TTNT, and OS. After balancing both treatment cohorts using IPTW, teclistamab demonstrated statistically significant and clinically superior results for ORR ≥CR rate, ≥VGPR rate, PFS, DoR, and TTNT, and numerically superior results for OS in the main analyses. The sections below present the results for the main analysis compared to the unadjusted analysis and sensitivity analyses.

7.5.3.1 Progression-free Survival

Unadjusted comparison results for PFS were compared to adjusted results from the main analysis (Figure 10). The unadjusted analysis found an HR of 0.52 (95% CI: 0.40, 0.67; $P < 0.0001$). Results from the main analysis using IPTW with ATT weights were statistically significantly in favor of teclistamab, with an HR of 0.48 (95% CI: 0.35, 0.64; $P < 0.0001$). Similar results were obtained across the sensitivity analyses.

Figure 10: Summary of Results for PFS

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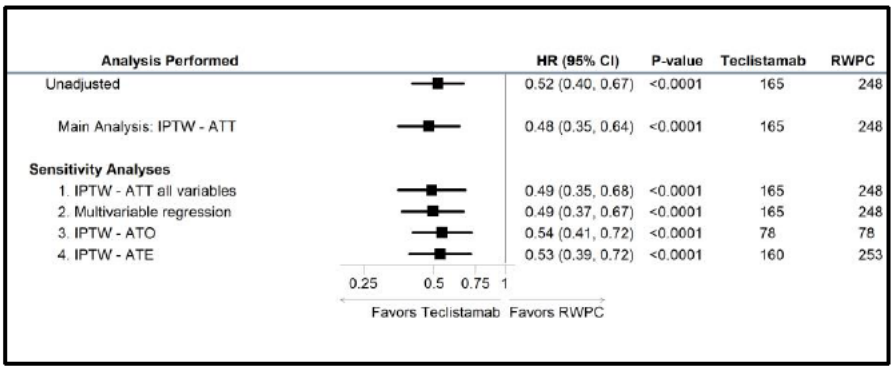
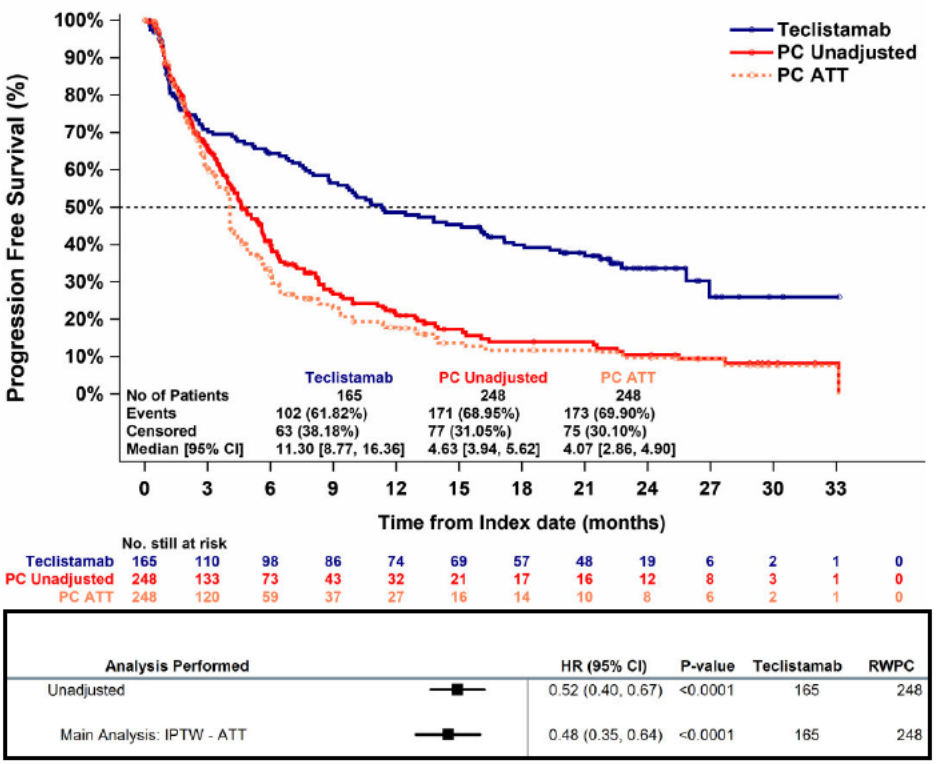


Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. HR<1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PFS, progression-free survival

7.5.3.1.1 Kaplan–Meier Analyses

The unadjusted and ATT weighted Kaplan–Meier plots for PFS are presented in Figure 11. The MajesTEC-1 population had a median PFS of 11.30 months (95% CI: 8.77, 17.15). In the unadjusted population, the median PFS for the physician's choice cohort was 4.63 months (95% CI: 3.94, 5.62). Median PFS in the main analysis and the sensitivity analysis including variables with missing data for the adjusted physician's choice cohort was 4.07 months (95% CI: 2.86, 4.90) and 3.58 months (95% CI: 2.56, 6.01)..

Figure 11. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of PFS for the main analysis



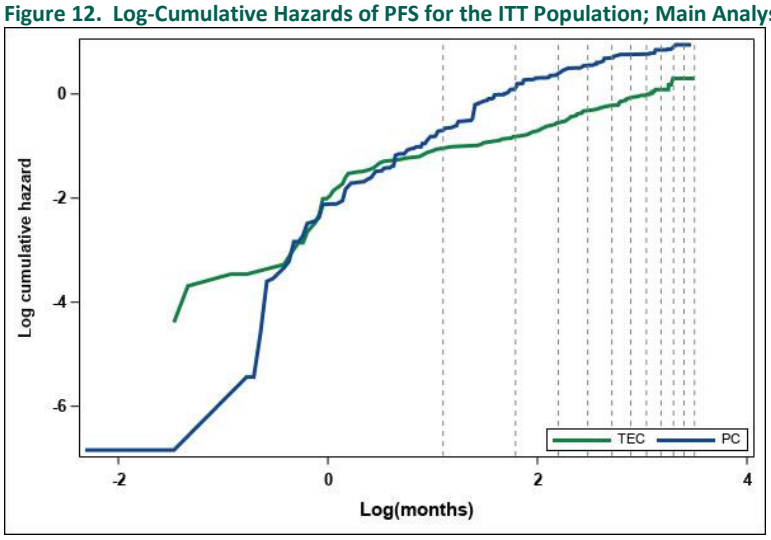
Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate

dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant.
Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; PFS, progression-free survival

7.5.3.1.2 Assessment of Proportional Hazards

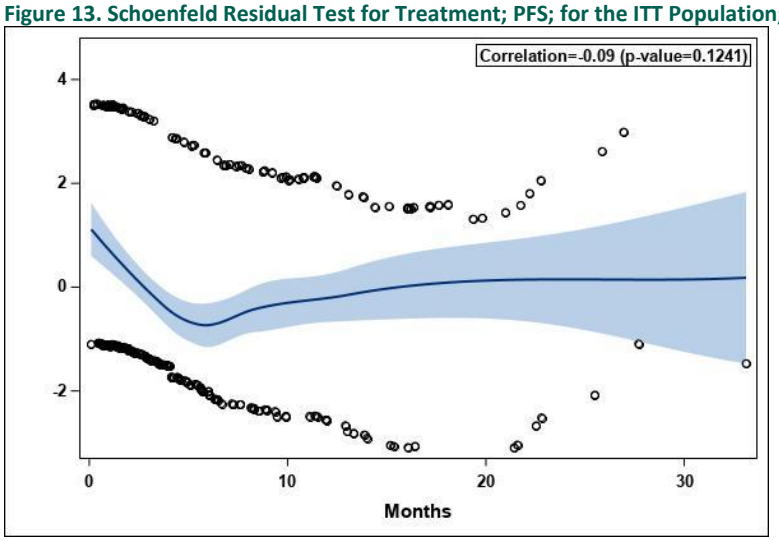
The proportional hazards assumption was assessed for the adjusted population in the main analysis. Visual inspection of the log-cumulative hazard plot (Figure 12) and Schoenfeld residuals plot for PFS (Figure 13) show evidence of potential violation of the proportional hazards assumption. The Grambsch-Therneau test for proportional hazards assumption was conducted and not found to be significant (p-value of 0.1241), indicating a potential confirmation of the proportional hazards assumption. The HR for PFS was 0.48 (95% CI: 0.35, 0.64) *p<.0001*.

Figure 12. Log-Cumulative Hazards of PFS for the ITT Population; Main Analysis



Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

Figure 13. Schoenfeld Residual Test for Treatment; PFS; for the ITT Population; Main Analysis



Grambsch-Therneau test: *p*-value: 0.1241
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival

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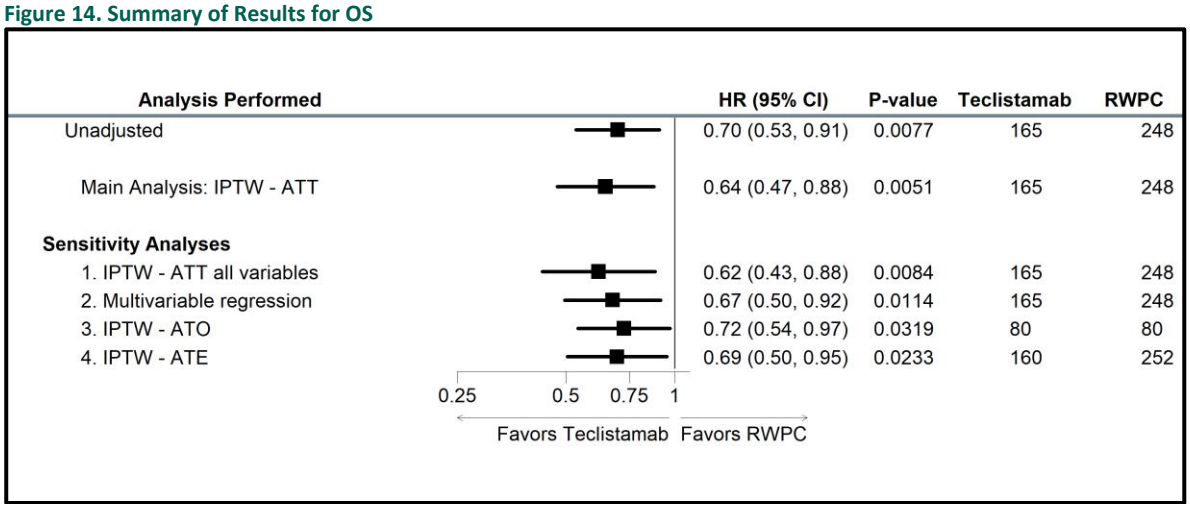
7.5.3.2 Overall Survival

Unadjusted comparison results for OS were compared to adjusted results from the main analysis (Figure 14). The unadjusted analysis found an HR of 0.70 (95% CI: 0.53, 0.91; *P* = 0.0077). Results from the main analysis using IPTW with ATT weights were statistically significant in favor of teclistamab, with an HR of 0.64 (95% CI: 0.46, 0.88; *P* = 0.0055). Similar results were obtained across the sensitivity analyses.

Figure 14. Summary of Results for OS

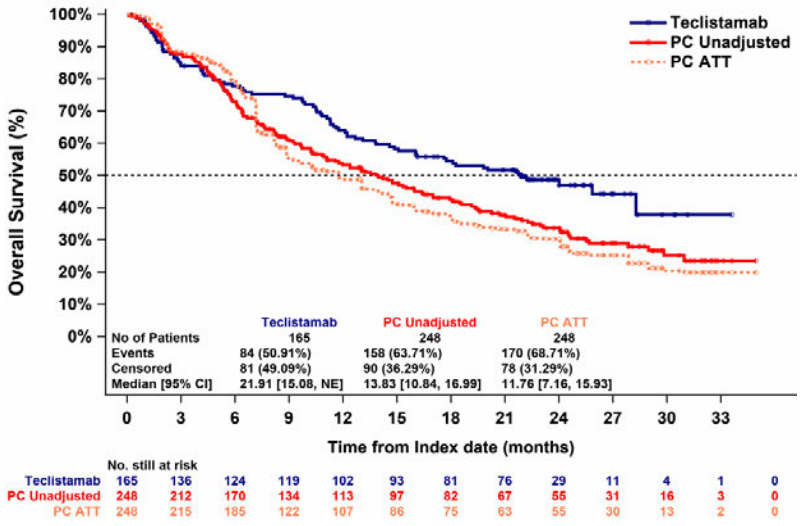


Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. HR<1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival

7.5.3.2.1 Kaplan–Meier Analyses

The unadjusted and ATT weighted Kaplan–Meier plots for OS are presented in Figure 15. The MajesTEC-1 population had a median OS of 21.91 months (95% CI: 15.08, NE). In the unadjusted population, the median OS for the physician's choice cohort was 13.83 months (95% CI: 10.84, 16.99). Median OS in the main analysis and the sensitivity analysis including variables with missing data for the adjusted physician's choice cohort were 11.76 months (95% CI: 7.16, 15.93), and 9.23 months (95% CI: 7.13, 14.75), respectively.

Figure 15. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of OS for the main analysis



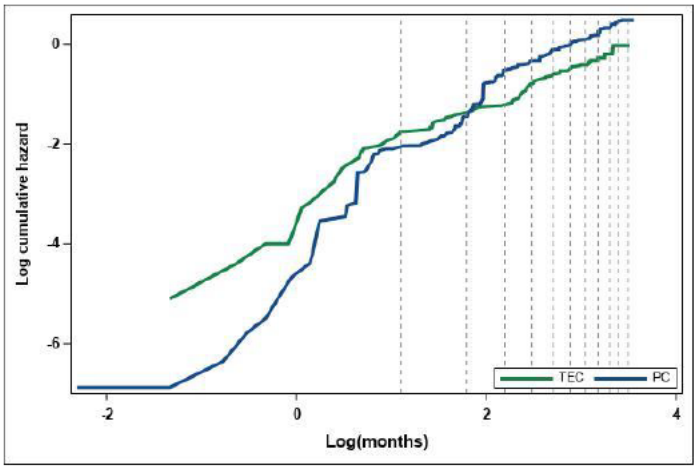
Analysis Performed	HR (95% CI)	P-value	Teclistamab	RWPC
Unadjusted	0.70 (0.53, 0.91)	0.0077	165	248
Main Analysis: IPTW - ATT	0.64 (0.46, 0.88)	0.0055	165	248

Main analysis adjusted for refractory status, International Staging System 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, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; NE, not evaluable; OS, overall survival.

7.5.3.2.2 Assessment of Proportional Hazards

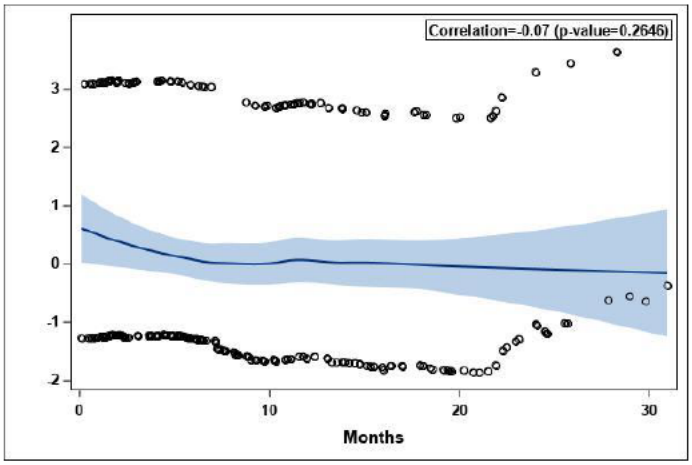
The proportional hazards assumption was assessed for the adjusted population in the main analysis. Visual inspection of the log-cumulative hazard plot (Figure 16) and Schoenfeld residuals plot (Figure 17) shows evidence of potential violation of the proportional hazards assumption prior to significant participant drop-off. However, the Grambsch-Therneau test for proportional hazards assumption was conducted and found to be non-significant (p-value of 0.2646), indicating the proportional hazards held. The HRs for OS was 0.64 (95% CI: 0.47, 0.88) *p=0.0051*.

Figure 16. Log-Cumulative Hazards of OS for the ITT Population; Main Analysis



Abbreviations: ITT, intention-to-treat; OS, overall survival

Figure 17. Schoenfeld Residual Test for Treatment; OS; for the ITT Population; Main Analysis



Grambsch-Therneau test: *p*-value: 0.2646
Abbreviations: ITT, intention-to-treat; OS, overall survival.

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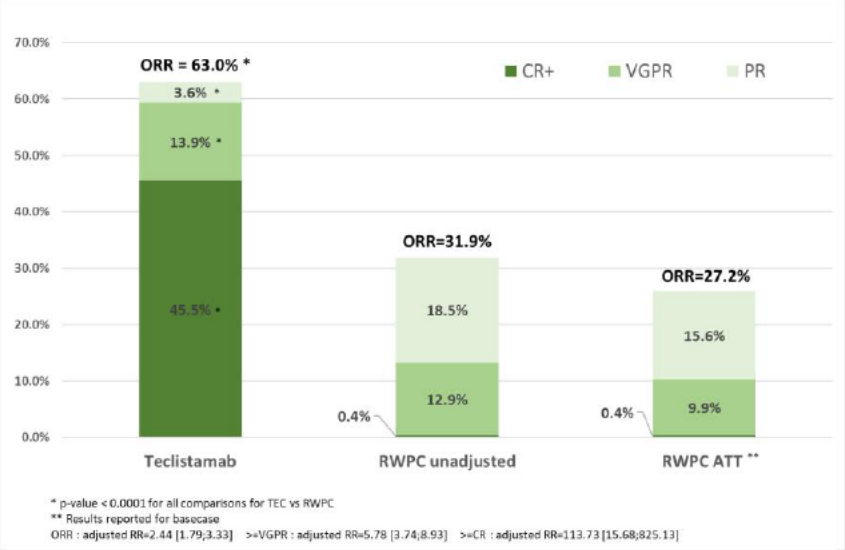
7.5.3.3 Response Rates

A summary of the results for the response rates for teclistamab and physicians' choice in the adjusted analysis and the unadjusted analysis is shown in. The ORR for teclistamab was 63% and for physicians' choice 31.9% and 27.2% in the unadjusted and adjusted analysis. For teclistamab CR, VGPR and PR was 45.5% 13.9% and 3.6% compared to physicians' choice 0.4%, 12.9% and 18.5 for the unadjusted and 0.4%, 9.9% and 15.6% for the adjusted analysis.

Figure 18. Summary of Results for Response rates



7.5.3.3.1 Overall response rate

The unadjusted comparison results for ORR were compared to the adjusted results from the main analysis (

Figure 19). The unadjusted analysis found an OR of 3.65 (95% CI: 2.41, 5.52; *P* < 0.0001) and a RR of 1.98 (95% CI: 1.48, 2.65). The results from the adjusted main analysis was statistically significantly in favor of teclistamab, with an OR of 4.89 (95% CI: 3.19, 7.47; *P* < 0.0001) and an RR of 2.44 (95% CI: 1.79, 3.33).

Figure 19. Summary of Results for Overall response rates

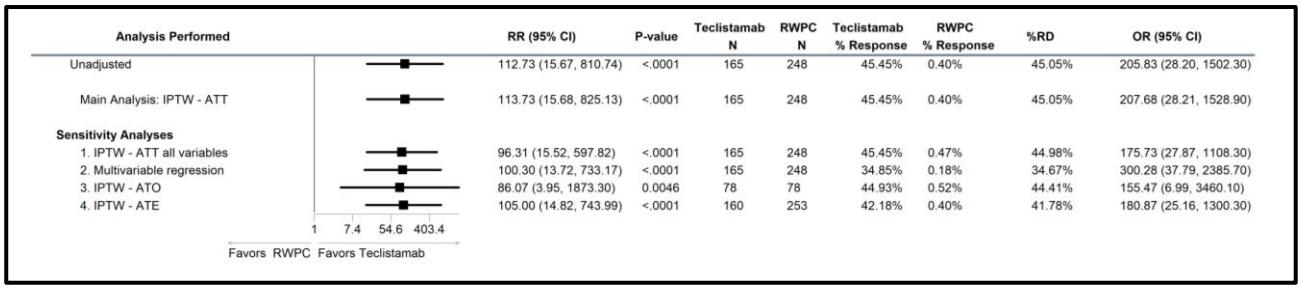
Analysis Performed	RR (95% CI)	P-value	Teclistamab N	RWPC N	Teclistamab % Response	RWPC % Response	%RD	OR (95% CI)
Unadjusted	1.98 (1.48, 2.65)	<.0001	165	248	63.03%	31.85%	31.18%	3.65 (2.41, 5.52)
Main Analysis: IPTW - ATT	2.44 (1.79, 3.33)	<.0001	165	248	63.03%	25.87%	37.16%	4.89 (3.19, 7.47)
Sensitivity Analyses								
1. IPTW - ATT all variables	2.43 (1.78, 3.32)	<.0001	165	248	63.03%	25.89%	37.14%	4.88 (3.19, 7.47)
2. Multivariable regression	1.98 (1.42, 2.74)	<.0001	165	248	56.01%	21.74%	34.27%	4.58 (2.75, 7.65)
3. IPTW - ATO	2.03 (1.24, 3.32)	0.0046	78	78	61.61%	30.30%	31.31%	3.69 (1.90, 7.16)
4. IPTW - ATE	1.98 (1.46, 2.69)	<.0001	160	253	58.30%	29.39%	28.91%	3.36 (2.22, 5.09)

Note: Main analysis adjusted for refractory status, International Staging System 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, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. OR>1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; OR, odds ratio; IPTW, inverse probability of treatment weighting; ORR, overall response rate; RD, rate difference; RR, response-rate ratio

7.5.3.3.2 Complete Response or Better Rate

The unadjusted comparison results for ≥CR rate were compared to adjusted results from the main analysis (Figure 20). The unadjusted analysis found an OR of 205.83 (95% CI: 28.20, 1502.30; P < 0.0001) and a RR of 112.73 (95% CI: 15.67, 810.74; P < 0.0001). Results from the main analysis were statistically significantly in favor of teclistamab, with an OR of 207.68 (95% CI: 28.21, 1528.90; *P* < 0.0001) and a RR of 113.73 (95% CI: 15.68, 825.13; p <0.0001). Similar results were obtained across the sensitivity analyses.

Figure 20. Summary of results for ≥CR Rate



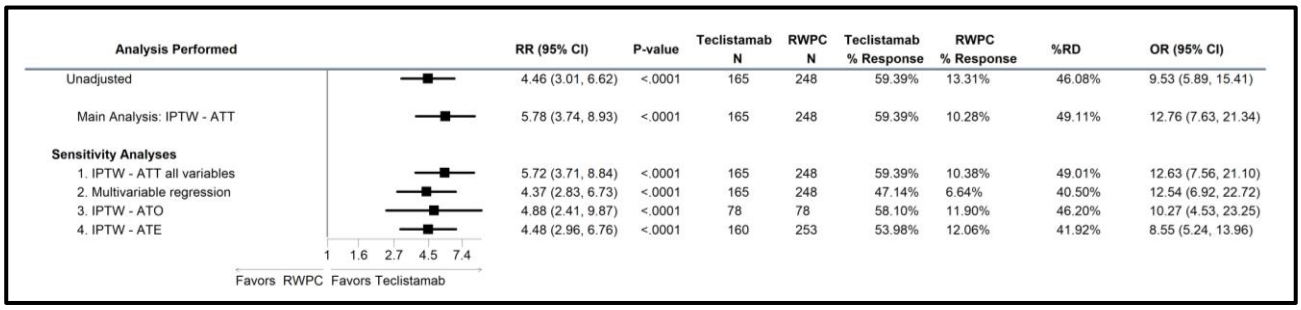
Analysis Performed	RR (95% CI)	P-value	Teclistamab N	RWPC N	Teclistamab % Response	RWPC % Response	%RD	OR (95% CI)
Unadjusted	112.73 (15.67, 810.74)	<.0001	165	248	45.45%	0.40%	45.05%	205.83 (28.20, 1502.30)
Main Analysis: IPTW - ATT	113.73 (15.68, 825.13)	<.0001	165	248	45.45%	0.40%	45.05%	207.68 (28.21, 1528.90)
Sensitivity Analyses								
1. IPTW - ATT all variables	96.31 (15.52, 597.82)	<.0001	165	248	45.45%	0.47%	44.98%	175.73 (27.87, 1108.30)
2. Multivariable regression	100.30 (13.72, 733.17)	<.0001	165	248	34.85%	0.18%	34.67%	300.28 (37.79, 2385.70)
3. IPTW - ATO	86.07 (3.95, 1873.30)	0.0046	78	78	44.93%	0.52%	44.41%	155.47 (6.99, 3460.10)
4. IPTW - ATE	105.00 (14.82, 743.99)	<.0001	160	253	42.18%	0.40%	41.78%	180.87 (25.16, 1300.30)

Note: Main analysis adjusted for refractory status, International Staging System 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, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. OR>1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; CR, complete response; OR, odds ratio; IPTW, inverse probability of treatment weighting; RD, rate difference; RR, response-rate ratio

7.5.3.3.3 Very Good Partial Response or Better Rate

The unadjusted comparison results for ≥VGPR rate were compared to adjusted results from the main analysis (Figure 21). The unadjusted analysis found an OR of 9.53 (95% CI: 5.89, 15.41; *P* < 0.0001) and an RR of 4.46 (95% CI: 3.01, 6.62). Results from the main analysis using IPTW with ATT weights were statistically significantly in favor of teclistamab, with an OR of 12.76 (95% CI: 7.63, 21.34; *P* < 0.0001) and an RR of 5.78 (95% CI: 3.74, 8.93). Similar results were obtained across the sensitivity analyses.

Figure 21. Summary of Results for ≥VGPR

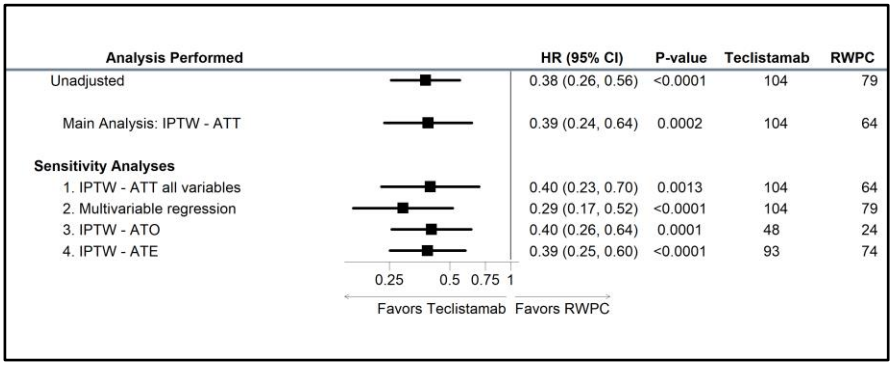


Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. OR>1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; OR, odds ratio; IPTW, inverse probability of treatment weighting; RD, rate difference; RR, response-rate ratio; ≥VGPR, very good partial response or better

7.5.3.4 Duration of Response

Unadjusted comparison results for DoR were compared to adjusted results from the main analysis (Figure 22). The unadjusted analysis found an HR of 0.38 (95% CI: 0.26, 0.56; *P* < 0.0001). Results from the main analysis using IPTW with ATT weights were statistically significantly in favor of teclistamab, with an HR of 0.39 (95% CI: 0.24, 0.64; P = 0.0002). Similar results were obtained across the sensitivity analyses. The multivariable regression analysis slightly differed, further favoring teclistamab. This could be explained by the differences in population used for DoR, where balance could be violated in the subset of patients that responded.

Figure 22. Summary of Results for DoR

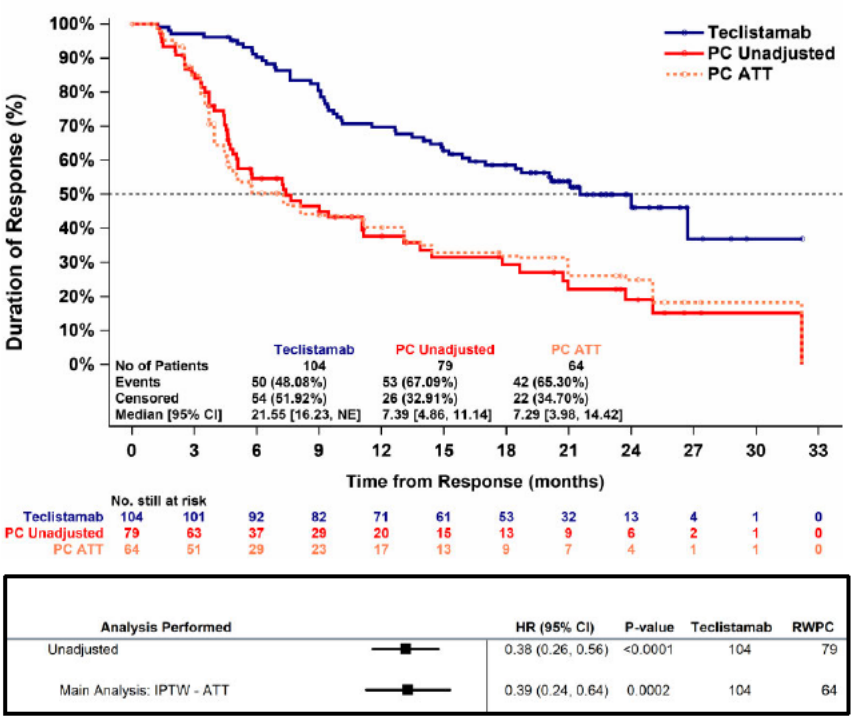


Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. HR<1 indicates favorable treatment effect for teclistamab. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; DoR, duration of response; HR, hazard ratio; IPTW, inverse probability of treatment weighting

7.5.3.4.1 Kaplan–Meier Analyses

The unadjusted and ATT weighted Kaplan–Meier plots for DoR are presented in Figure 23. The median DoR was 21.55 months (95% CI: 16.23, NE) for the MajesTEC-1 population. In the unadjusted population, the median DoR for the physician's choice cohort was 7.39 months (95% CI: 4.86, 11.14). The median DoR for the main analysis and the sensitivity analysis including variables with missing data for the physician's choice cohort were 7.39 months (95% CI: 4.86, 11.14) and 5.78 months (95% CI: 3.32, 20.96), respectively.

Figure 23. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of DoR for main analysis



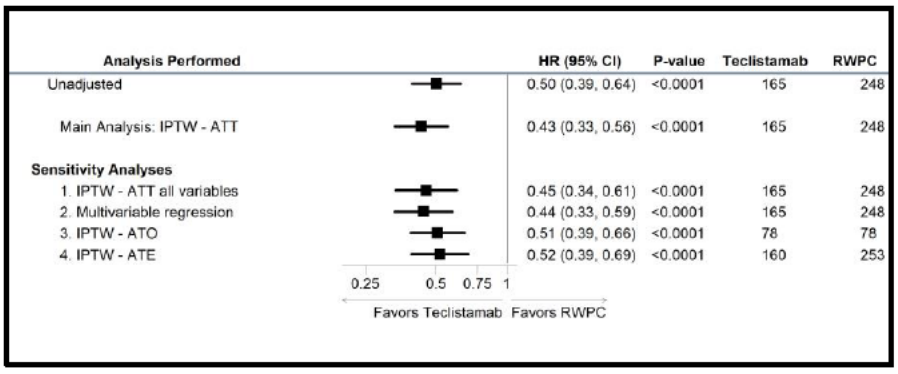
Analysis Performed	HR (95% CI)	P-value	Teclistamab	RWPC
Unadjusted	0.38 (0.26, 0.56)	<0.0001	104	79
Main Analysis: IPTW - ATT	0.39 (0.24, 0.64)	0.0002	104	64

Main analysis adjusted for refractory status, International Staging System 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, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; DoR, duration of response; NE, not evaluable

7.5.3.5 Time to Next Treatment

Unadjusted comparison results for TTNT were compared to adjusted results from the main analysis (Figure 24). The unadjusted analysis found an HR of 0.50 (95% CI: 0.39, 0.64; $P < 0.0001$). Results from the main analysis using were statistically significantly in favor of teclistamab, with an HR of 0.43 (95% CI: 0.33, 0.56; $P < 0.0001$). Similar results were obtained across all the sensitivity analyses.

Figure 24. Summary of Results for TTNT

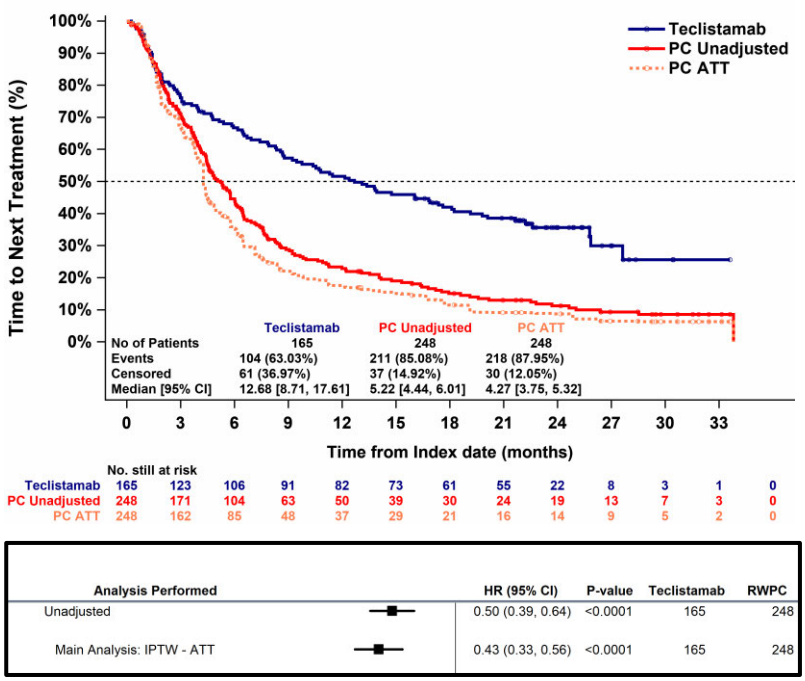


Note: Main analysis adjusted for refractory status, International Staging System stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of therapy, years since multiple myeloma diagnosis, average duration of prior lines, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis. Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; TTNT, time to next treatment

7.5.3.5.1 Kaplan–Meier Analyses

The unadjusted and ATT weighted Kaplan–Meier plots for TTNT are presented in Figure 25. The MajesTEC-1 population had a median TTNT of 12.68 months (95% CI: 8.71, 17.61). In the unadjusted population, the median TTNT for the physician's choice cohort was 5.22 months (95% CI: 4.44, 6.01). The median TTNT for the main analysis and was 4.27 months (95% CI: 3.75, 5.32) and 4.27 months (95% CI: 2.89, 6.18), respectively.

Figure 25. Unadjusted and Adjusted (ATT Weighted) Kaplan–Meier Plots of TTNT for the main Analysis



Analysis Performed	HR (95% CI)	P-value	Teclistamab	RWPC
Unadjusted	0.50 (0.39, 0.64)	<0.0001	165	248
Main Analysis: IPTW - ATT	0.43 (0.33, 0.56)	<0.0001	165	248

Main analysis adjusted for refractory status, International Staging System 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, age, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group score, sex, type of multiple myeloma, and prior stem cell transplant. Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; NE, not evaluable; TTNT, time to next treatment.

7.5.4 Patient reported outcomes comparative analyses (EQ5D-5L and EORTC QLQ-C30)

Comparative analyses for PRO's were not available. However, a recent poster presented at the European Hematology Association (EHA) congress in June 2023 provides the best available comparative analyses[1].The included data differed slightly from the other analyses presented in this dossier: The same datacuts for MajesTEC-1 and LocoMMotion were utilized, but only the phase 2 portion of MajesTEC-1 (N=125, enrolled Oct 2020–Aug 2021; clinical cut-off, Jan 4, 2023).

Statistical analyses

Differences in changes from baseline (CFB) between treatment cohorts were estimated using a mixed model of repeated measures (MMRM), including baseline prognostic variables as covariates to adjust for confounding bias.

- MMRM analyses included patients with baseline and post baseline PRO assessments (teclistamab, n=85; RWPC, n=170)

[1] Poster has been supplied to the Danish Medicines Council and can be accessed here: https://www.congresshub.com/Oncology/EHA2023/Teclistamab/Moreau-Patient-Reported

PRO assessments were mostly available before progression and mostly missing after progression; the MMRM approach does not account for the selective dropout of patients who progressed or died, which may underestimate the PRO benefit of teclistamab due to its longer progression-free survival and overall survival vs RWPC.

- To correct for this inherent survival bias, a responder analysis was performed for each PRO domain. Patients who progressed or died were put in a separate category, whereas progression-free patients were classified as having meaningful improvement, no improvement/worsening, or worsening based on predefined threshold of ≥10 points on a 1–100 scale over time.

Results

[redacted]

Table 21 Mean changes from baseline in PROs for teclistamab vs RWPC

PRO domain	CFB[a] for individual therapies		Difference in CFB[a] teclistamab vs RWPC
	Teclistamab (n=85)	RWPC (n=170)	
[redacted]			

*P<0.05; **P<0.01. [a]Absolute improvement on 0–100 scale; data collected at baseline and on day 1 of every other treatment cycle up to cycle 16. [b]Positive values represent improvement; positive difference in CFB favors teclistamab. [c]Negative values represent improvement; negative difference in CFB favors teclistamab. CFB, change from baseline.

7.5.5 Safety results comparative analyses

The safety inputs for the health economic assessment were based on the MajesTEC-1 trial and the LocoMMotion trial for teclistamab and physician's choice respectively. Table 22 includes an overview of relevant and the most common (≥5% of subjects) grade 3 or 4 TEAEs for teclistamab and physician's choice. In the health economic analysis, TEAEs were included as they affect both costs and quality of life of patients receiving treatment.

AEs were only considered for the initial treatment but not for subsequent treatments. Except for CRS in MajesTEC-1, AEs rates were limited in the CE-model to those of grade 3 or higher that had occurred in at least 5% of all treated patients in MajesTEC-1 or LocoMMotion. For CRS, Grade 1-2 events were included as well as Grade 3+, and no minimum incidence criterion was used.

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Table 22. Incidence rates of adverse events (Grade 3-4 in ≥5% of subjects unless other specified)

Adverse events	Teclistamab MajesTEC-1[25]	Physician's choice LocoMMotion[75]
Total number of participants with TEAE	**165 (100.0%)**	**215 (86.7%)**
Grade 3-4	**156 (94.5%)**	**144 (58.1%)**
Grade 3-4 in ≥5% of subjects		
Anemia	37.6%	10.9%
CRS, Grade 1-2	71.5%	0.0%
CRS, Grade 3+	0.6%	0.0%
Hypertension	6.1%	2.4%
Hypophosphatemia	6.7%	0.0%
Leukopenia	9.1%	6.0%
Lymphopenia	34.5%	7.7%
Neutropenia	65.5%	17.3%
Pneumonia	13.3%	2.4%
Thrombocytopenia	22.4%	19.4%

8. Health economic analysis

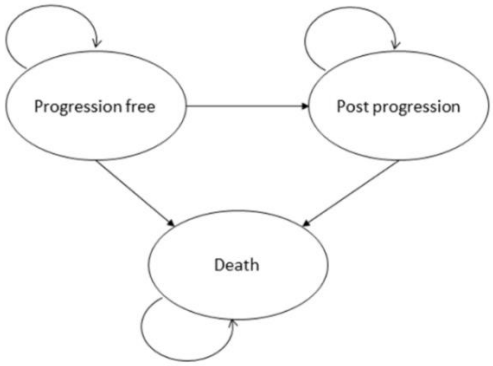
To capture the costs and outcomes of treating RRMM over a lifetime time horizon in Denmark and evaluate the value of teclistamab versus physician's choice in triple class exposed RRMM a partitioned survival model (PSM) was developed and adapted to the Danish setting. Adaptations to the model were made to fit the requirements for health economic assessments in Denmark.

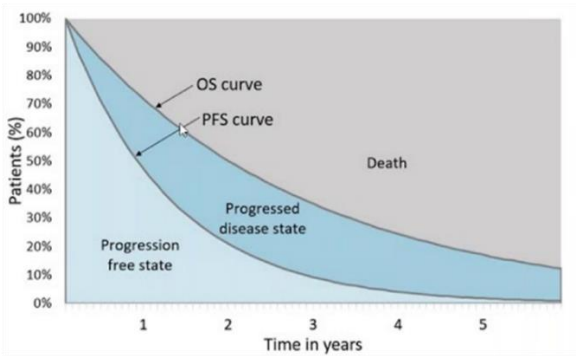
8.1 Model

8.1.1 Model structure

The CEM followed the structure of a PSM and included three health states: progression-free, post-progression and death, which were defined by overall survival (OS) and progression-free survival (PFS) using the area under the curve approach (Figure 26). The progression-free state included all patients who either had stable disease or responded to therapy. The post-progression state included patients with progressed disease (as defined in MajesTEC-1) [25]. All patients were assumed to enter the model progression free. From the progression-free 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 progression-free 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.

Figure 26. PSM structure





8.1.1.1 Rationale for model approach

The model structure represents a simplification of the clinical pathway and care of patients with RRMM but is believed to be suitable for decision making in the Danish setting. The PSM structure was selected due that it is widely used in oncology, with guidance from NICE's Decision Support Unit available on this decision modelling tool [76] and for the DMC in particular (Table 23). The previous economic assessments were identified by a targeted search of the DMC website.

In addition, the PSM captures key elements of the disease process from clinical, patient and costing perspectives, including disease progression and survival, and is suited to the natural history of MM, whereby patients move forwards through a set of health states. As patients receive active therapy, treatment-specific acquisition, administration, resource use and AE costs are incurred. Costs associated with subsequent treatment are also captured in the 'post-progression' state. As evidence suggests that patients' HRQoL declines permanently upon disease progression [77] and transiently if certain AEs occur [78]; the current model structure allows the variation in HRQoL over time to be captured through health-state-specific utility values and utility decrements associated with AEs.

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Table 23. Model structures in previous assessments in RRMM or MM

Treatment	Treatment line	Model structure	Health states	Year
Isatuximab, carfilzomib, and dexamethasone	Second-line (RRMM)	PSM	PFS on treatment, PFS off treatment, PD, Dead	2022 [79]
Daratumumab in combination with bortezomib, thalidomide, and dexamethasone	First-line (MM)	PSM	PFS, PD, Dead	2021 [80]
Daratumumab in combination with bortezomib, melphalan and prednisone	First-line (MM)	PSM	PFS, PD, Dead (patients are either on or off treatment in the PFS/PD health states)	2022 [81]
Isatuximab in combination with pomalidomide and dexamethasone	Third line	PSM (simplified)	PFS on treatment, PFS off treatment	2020 [82]
Elotuzumab in combination with pomalidomide and dexamethasone	Third line	PSM	PFS, PD, Dead	2020 [83]
Pomalidomide in combination with bortezomib and dexamethasone	Second line	Not clear	PFS on or off treatment	2019 [84]
Lenalidomide in combination with bortezomib and dexamethasone	First line	Not clear	PFS on or off treatment	2019 [85]
Lenalidomide	First-line RRMM	Not clear	PFS on first-line treatment/Progression on subsequent treatment	2019 [86]

The model structure is able to capture the main difference in benefits (duration of PFS, harm through adverse reactions, and OS) and costs (dominated by treatment costs in the "PF" health state between intervention and comparator). Patient preference and ultimately the quality adjusted life years (QALYs) gained per treatment is captured with utility or health related index scores per health state. Additionally, it is a strength that the model structure is consistent with decision models in RRMM considered by the DMC in the assessment of previously available treatments (see Table 23).

8.1.2 Population

The population for the analysis was based on the trial population from MajesTEC-1 [68] and is representative of the eligible population in Denmark.

8.1.3 Intervention

Teclistamab is an off-the-shelf, T-Cell redirecting, bispecific antibody targeting both BCMA and CD3 receptors. BCMA is expressed at high levels on multiple myeloma cells. Teclistamab redirects CD3-positive T-cells to BCMA-expressing myeloma cells to induce killing of tumor cells [67]. Teclistamab is indicated for the treatment of adult patients with RRMM, who have 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.

8.1.4 Comparator

In the Danish treatment guidelines for MM, there is no recommendation for any single regimen or combination regimen for the specific population indicated for treatment with teclistamab (see further Section 5.2). The most relevant comparator to teclistamab in Denmark was thus considered to be a combination of available and used regimens for the treatment of ≥4th line RRMM, henceforth called 'physician's choice'. The composition of the physician's choice basket was, cost-wise, based on the DMC evaluation report of ciltacabtagen-autoleucel. The efficacy outcomes of physician's choice included in the CEM were based on the LocoMMotion comparative dataset. The composition of physician's

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choice has previously been presented in section 5.3, while LocoMMotion and its comparison to MajesTEC-1 were previously presented in section 7.2, 7.4, and 7.5. (See also section 18.1.5 Table 70)

8.1.5 Outcomes

The model estimated total costs for the treatment with teclistamab and for physician's choice. Benefit and harm of treatments was measured using LYs and QALYs. Incremental differences were reported and summarized using ICERs.

8.1.6 Perspective

The base case analysis included a Danish limited societal perspective that included both direct treatment costs, healthcare utilization costs and non-medical costs i.e., transportation costs and time spent in connection with treatment for the patients. Caregiver cost and utility was not implemented in the base case but caregiver cost was tested in a scenario analysis.

8.1.7 Cycle length and half cycle correction

A cycle length of one week was used for the analysis as this allows capturing the varied dosing schedules of therapies that make up the physician's choice comparator. A half-cycle correction is applied to the calculation of costs and health effects accrued throughout each cycle, 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).

8.1.8 Time horizon

According to the Danish guidelines, the time horizon should be long enough to capture the all significant differences in outcomes and costs between the intervention and the comparator [87]. A lifetime time horizon should be used when the treatment is believed to extend life [87]. The model has the flexibility to select a time horizon between 1 and 40 years. The selected time horizon in the base case was 40 years, which is long enough to ensure that all costs and benefits associated with treatment were captured as this corresponded to a lifetime perspective for the modelled cohort. Different time horizons were tested in scenario analysis.

8.1.9 Discount rates

Both costs and health effects were discounted at a rate of 3,5% per year for the first 35 years and with 2,5% between 35 and 40 years, in accordance with the current discount rates in Denmark [87, 88]. Different discount rates for cost and effects were tested in scenario analysis.

8.1.10 Uncertainty

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty. Parameter uncertainty was assessed in the univariate (one-way) deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). In addition, a series of scenario analyses was conducted to test the robustness of the model.

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8.1.11 Key assumptions used in the analysis

The base case settings applicable to the Danish setting are provided in Table 24.

Table 24. Base case settings

Setting	Base case for model adaptation	
Model Structure	PSM	
Population	ITT	
Time horizon	Lifetime	
Intervention	Teclistamab	
Comparator	Physician's choice	
Teclistamab data source	MajesTEC-1 data-cut January 2023	
Physician's choice data source	LocoMMotion efficacy data-cut November 2021	
Regimen distribution in physician's choice	Kd	33.3%
	Pd	33.3%
	PVd	33.3%
Teclistamab survival parametrization OS	Lognormal	
Teclistamab survival parametrization PFS	Lognormal	
Physician's choice parametrization OS	Lognormal	
Physician's choice parametrization PFS	Lognormal	

Abbreviations: Kd=Carfilzomib plus dexamethasone; Pd=Pomalidomide plus dexamethasone; PVd= Pomalidomide plus bortezomib plus dexamethasone.

8.1.12 Limitations

The limitations of the PSM structure arise when there is uncertainty around long-term PFS and OS extrapolations. The extrapolation of short-term results over a lifetime horizon inherently introduces uncertainty into the results. Long-term survival outcomes with teclistamab are subject to uncertainty considering the relatively low event rate (49.09% censored for OS) and the lack of long-term clinical experience with teclistamab.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The input data with regards to clinical effectiveness, adverse reactions and quality of life inputs used for the base case was mainly derived from the pivotal trial MajesTEC-1, the LocoMMotion trial and literature. Where needed, data was extrapolated based on goodness-fit statistics and clinical plausibility. A summary of included clinical inputs is presented in Table 25. Summary of included clinical inputs.

Table 25. Summary of included clinical inputs

Name of estimates	Value	Source
Baseline characteristics		
Age, mean (SD)	63.9 (9.6)	MajesTEC-1
Proportion female	41.8%	MajesTEC-1
Body weight, mean (SD)	75 (16.7)	MajesTEC-1
Body surface area, mean (SD)	1.83 (0.24)	MajesTEC-1
Survival analysis		
PFS intervention		Parametrization based on goodness-of-fit and clinical plausibility
PFS comparator		Parametrization based on goodness-of-fit and clinical plausibility
OS intervention		Parametrization based on goodness-of-fit and clinical plausibility
OS comparator		Parametrization based on goodness-of-fit and clinical plausibility
Health state utilities		
Progression-free (Cycle 0)	0.639	MajesTEC-1
Progression-free (Cycle 2)	0.689	MajesTEC-1
Progression-free (Cycle 4)	0.740	MajesTEC-1
Progression-free (Cycle 6)	0.743	MajesTEC-1
Progression-free (Cycle 8)	0.770	MajesTEC-1
Progression-free (Cycle 10)	0.761	MajesTEC-1
Progression-free (Cycle 12)	0.757	MajesTEC-1
Progression-free (Cycle 14)	0.755	MajesTEC-1
Progression-free (Cycle 16)	0.775	MajesTEC-1
Progression-free (Cycle 18)	0.758	MajesTEC-1
Progression-free (Cycle 20)	0.811	MajesTEC-1
Progression-free (Cycle 22)	0.792	MajesTEC-1
Progression-free (Cycle 24)	0.792	MajesTEC-1
Progressed disease	0.670	MajesTEC-1
Adverse events		
Anemia	37.6%/10.9%	MajesTEC-1/LocoMMotion
CRS only, Grade 1-2	71.5%/0%	MajesTEC-1
CRS only, Grade 3+	0.6%	MajesTEC-1/LocoMMotion
Hypertension	5.5%/2.4%	MajesTEC-1/LocoMMotion
Hypophosphatemia	6.1%/0%	MajesTEC-1/LocoMMotion
Leukopenia	9.1%/6.0%	MajesTEC-1/LocoMMotion
Lymphopenia	34.5%/7.7%	MajesTEC-1/LocoMMotion
Neutropenia	65.5%/17.3%	MajesTEC-1/LocoMMotion
Pneumonia	13.3%/0%	MajesTEC-1/LocoMMotion
Thrombocytopenia	21.4%/19.4%	MajesTEC-1/LocoMMotion

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8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

8.2.2.1.1 Danish clinical practice

In Denmark, the median age at diagnosis is 70 years in MM patients [89], while the mean age in MajesTEC-1 is 63,9 years. We do not have access to data for Danish triple class exposed RRMM patients, but we speculate that these patients may be younger than the median patient at diagnosis because patients that are younger at diagnosis have a greater chance of surviving until 3rd line of treatment. Therefore, we expect the results from MajesTEC-1 to be generalizable to a Danish population.

8.2.2.1.2 Clinical documentation submitted (in relation to clinical practice)

The baseline characteristics for the overall eligible population used in the CEM was based on the MajesTEC-1 trial population: adult patients with RRMM who had ≥3 prior lines of therapy including a PI, IMiD and an anti-CD38 and who had disease progression on the last regimen. Baseline characteristics from the trials are presented in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

In the adjusted treatment comparison between teclistamab (MajesTEC-1) and physician's choice (LocoMMotion) (see section 7.5) the ITT populations were considered analogous and were compared. To ensure a balance in baseline characteristics between participants in the MajesTEC-1 and physician's choice cohorts at the index date, selected prognostic factors were adjusted for using either propensity score or regression methods. The main analysis 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 MM diagnosis, average duration of prior lines, age, hemoglobin levels, LDH levels, creatinine clearance, ECOG status, sex, type of MM, and prior stem cell transplant. The sensitivity analysis including variables with missing data weighted participants on race and cytogenetic profile, in addition to variables from the main analysis.

8.2.2.1.3 Health economic analysis submitted

The baseline characteristics of all treated population used in the CEM is taken from MajesTEC-1 and are presented in Table 26. The mean age of 64 at treatment initiation was assumed to be representative for the Danish patient population relevant for this treatment.

Table 26. Patient population

Patient population Important baseline characteristics	Clinical documentation	Used in the model	Danish clinical practice*
Age, mean (SD)	63.9 (9.6)	63.9 (9.6)	64
Proportion female	41.8%	41.8%	41.8%
Body weight, mean (SD)	75 (16.7)	75 (16.7)	75 (16.7)
Body surface area, mean (SD)	1.83 (0.24)	1.83 (0.24)	1.83 (0.24)

*Validated by a Danish clinical expert [60].

8.2.2.2 Intervention

8.2.2.2.1 Danish clinical practice

The intervention, teclistamab, previously described (Section 5.4) is expected to be used according to the approved indication and in the relevant population described above, i.e., in adult patients with RRMM, who have received at least three prior therapies including a PI, IMiD and an anti-CD38 and who had disease progression on the last regimen.

8.2.2.2.2 Clinical documentation submitted

The key clinical documentation for the intervention is the pivotal trial MajesTEC-1. See Sections 7.1 and 7.3 for clinical efficacy and Section 7.5 for relative efficacy.

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8.2.2.2.3 Health economic analysis submitted

Inputs used in the cost-effectiveness analysis are primarily informed by the clinical trials MajesTEC-1, and clinical literature in combination with clinical expertise [60]. In the CEM treatment with teclistamab was administered based on MajesTEC-1 according to the recommended dosage of 1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule. In accordance with MajesTEC-1 and EMA approval, dosing switch—from weekly to bi-weekly dosing—was implemented in the base-case analysis. The switch occurs successively amongst certain patients, which is in line with the study (MajesTEC-1) but also the expectation for real-world-praxis in a Danish context. Teclistamab should be continued until disease progression or unacceptable toxicity. This is in line with the expected use of teclistamab in Denmark. A summary of the intervention is given in Table 27.

Table 27. Overview of intervention teclistamab

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	The dose is 1.5 mg per kg of body weight after top-up dosing administered subcutaneously. See section 5.4 for full details.	The dose is 1.5 mg per kg of body weight after top-up dosing administered subcutaneously. See section 5.4 and 8.5.1.1 for full details.	The dose is 1.5 mg per kg of body weight after top-up dosing administered subcutaneously. See section 5.4 for full details.
Length of treatment	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 9.4 months.	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 9.4 months.	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 9.4 months.
The pharmaceutical's position in the Danish clinical practice	Treatment of adults with RRMM who have received at least three prior therapies: PI, ImiD and anti-CD38 mAbs and had progressed on the last regimen.	Treatment of adults with RRMM who have received at least three prior therapies: PI, ImiD and anti-CD38 mAbs and had progressed on the last regimen.	Treatment of adults with RRMM who have received at least three prior therapies: PI, ImiD and anti-CD38 mAbs and had progressed on the last regimen.

8.2.2.3 Comparator

8.2.2.3.1 Danish clinical practice

In Denmark, the comparator to teclistamab was physician's choice, see further Section 5.2 and 5.3. A majority of patients participating in the LocoMMotion study were treated in an European context. As previously described, LocoMMotion was the most relevant comparative data source for Denmark for patients with RRMM matched to the population in MajesTEC-1 [75]. LocoMMotion was considered most relevant due to the inclusion criteria and the prospective trial design. In the base case analysis physician's choice was modelled as a blended comparator informed by the study LocoMMotion and the DMC evaluation report of ciltakabtagen-autoleucel, , to reflect the Danish clinical practice. For additional information see section 5.3 and 7.

8.2.2.3.2 Health economic analysis submitted

The insights into the treatment patterns in Denmark were provided by the DMC evaluation report of ciltakabtagen-autoleucel. Based on the survey results, assumptions have been made regarding the distribution of SoC regimens of physician's choice relevant for Denmark. Furthermore, LocoMMotion showed also that there is no clear regimen for SoC for the triple class exposed RRMM patient population. Further details on the frequency of regimens of physician's choice that were administered in LocoMMotion are presented in Appendix F, section 18.1.5.

In the CEM, treatment with physician's choice was administered based on the recommended SmPC dosage [62, 64, 65] or treatment guidelines [31, 61]. Treatment should be continued until disease progression or unacceptable toxicity. A summary of the comparator (Physician's choice) is given in Table 29.

Table 28. Physician's choice treatment mix based on LocoMMotion, relevant for Denmark

Therapy	%
Kd	21.0%33.3%
Pd	13.0%33.3%

PVd	33.3%
Total	**100%**

Abbreviations: Kd=Carfilzomib plus dexamethasone; Pd=Pomalidomide plus dexamethasone; PVd=Pomalidomide plus bortezomib plus dexamethasone.

Table 29. Overview of comparator physician's choice

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Kd	Carfilzomib 20/56 mg/m² IV Dexamethasone 20 mg PO	Carfilzomib 20/56 mg/m² IV Dexamethasone 20 mg PO	Carfilzomib 20/56 mg/m² IV Dexamethasone 20 mg PO
Pd	Pomalidomide 4 mg PO Dexamethasone 40 mg PO	Pomalidomide 4 mg PO Dexamethasone 40 mg PO	Pomalidomide 4 mg PO Dexamethasone 40 mg PO
PVd	Pomalidomide 4 mg PO Bortezomib 1.3 mg/m2 Dexamethasone 20 mg PO Venetoclax 1,200 mg PO	Pomalidomide 4 mg PO Bortezomib 1.3 mg/m2 Dexamethasone 20 mg PO Venetoclax 1,200 mg PO	Pomalidomide 4 mg PO Bortezomib 1.3 mg/m2 Dexamethasone 20 mg PO Venetoclax 1,200 mg PO
Length of treatment	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 3.7 months.	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 3.7 months	Provided until disease progression or toxicity-related to treatment. Median time to treatment discontinuation: 3.7 months
The comparator's position in the Danish clinical practice	Treatment of adults with RRMM who have received at least three prior LOTs including at least one PI, one IMiD and one anti-CD38 mAB	Treatment of adults with RRMM who have received at least three prior LOTs including at least one PI, one IMiD and one anti-CD38 mAB	Treatment of adults with RRMM who have received at least three prior LOTs including at least one PI, one IMiD and one anti-CD38 mAB

Abbreviations: D= Daratumumab; DVd= Daratumumab plus bortezomib plus dexamethasone; ERd= Elotuzumab plus lenalidomide plus dexamethasone; IRd= Ixazomib plus lenalidomide plus dexamethasone; IV=Intravenous; Kd=Carfilzomib plus dexamethasone; KRd= Carfilzomib plus lenalidomide plus dexamethasone; LOT= Line of therapy; Pd=Pomalidomide plus dexamethasone; PCd=Pomalidomide plus cyclophosphamide plus dexamethasone; PO= per oral; SC= Subcutaneous; Vd= Bortezomib plus dexamethasone; VCd= Bortezomib plus cyclophosphamide plus dexamethasone. Source: [61-65].

8.2.2.4 Relative efficacy outcomes

8.2.2.4.1 Clinical documentation submitted

The relative efficacy outcomes that were used to compare teclistamab with physician's choice were PFS and OS. Relative efficacy outcomes were based on data from an adjusted treatment comparison between teclistamab (MajesTEC-1) and physician's choice (LocoMMotion).

8.2.2.4.2 Danish clinical practice

The current treatment goals for RRMM focus on improving outcomes such as OS, PFS, and overall HRQoL. Both PFS and OS were included in MajesTEC-1 and LocoMMotion and are used in the health economic analysis. These endpoints are considered to reflect the Danish clinical practice.

8.2.2.4.3 Health economic analysis submitted

A CEM was used to analyze the cost-effectiveness of teclistamab in Denmark. The model was populated with key outcomes from the MajesTEC-1 and LocoMMotion studies. Table 30 includes the model values for PFS and OS used in the model and the median from MajesTEC-1 and LocoMMotion. Table 31 summarizes the relevance of the clinical outcomes for Danish clinical practice.

Table 30. Summary of value

Clinical efficacy outcome	Used in the model (value)	Clinical documentation
PFS	Lognormal extrapolation – an estimated mean for teclistamab of 41.93 months, and median 10.58 months. Physician's choice mean 7.73 months, and median 4.14 months.	Median PFS for teclistamab 11.30 (95% CI: 8.77, 16.36) months. Median PFS for physician's choice (based on LocoMMotion) 4.07 (95% CI: 2.86, 4.90) months.

OS	Lognormal extrapolation – an estimated mean for teclistamab of 59.9 months, and median 21.62 months. Physician's choice mean 23.28 months, and median 12.42 months.	Median OS for teclistamab 21.91 (95% CI: 15.08, NE). Median OS for physician's choice (based on LocoMMotion) 11.76 (95% CI: 7.16, 15.93) months.

Table 31. Summary of relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
PFS	Defined as duration from the index date to the date of first documented disease progression or death due to any cause, whichever occurred first. IMWG criteria for PD.	PFS represents a relevant outcome measure with regards to treatments for RRMM in Denmark.	Relevant
OS	Defined as the time from the index date to the date of the participant's death.	OS represents a relevant outcome measure with regards to treatments for RRMM in Denmark.	Relevant

8.2.2.5 Adverse reaction outcomes

8.2.2.5.1 Clinical documentation submitted

AEs are described and discussed in Sections 7. Data from MajesTEC-1 established a favorable benefit-risk profile for the use of teclistamab as a treatment for patients with RRMM whose prior therapy includes the three key classes of treatment in this population (i.e., a PI, IMiD, and anti-CD38 mAb). For physician's choice clinical documentation of AEs are based on LocoMMotion study where the most common TEAEs included blood and lymphatic system disorders. The grade 3 and 4 treatment emergent adverse events which occurred in MajesTEC-1 and LocoMMotion are presented in 7.3.7 and 7.4.2 respectively.

The safety inputs for the health economic assessment were based on the MajesTEC-1 trial. The safety for physician's choice was based on the LocoMMotion study. Section 7.5.5 includes an overview of relevant and the most common (≥5% of subjects) grade 3 or 4 TEAEs for teclistamab and physician's choice. In the health economic analysis, TEAEs were included as they affect both costs and quality of life of patients receiving treatment. AEs were only considered for the initial treatment but not for subsequent treatments. Except for CRS, AEs rates were limited to those of grade 3 or higher that had occurred in at least 5% of all treated patients in MajesTEC-1 or LocoMMotion.

Any grade 3 or 4 AEs identified for one treatment arm were included for the other as well, if data was available. For CRS, Grade 1-2 events were included as well as Grade 3+, and no minimum incidence criterion was used. In the CEM, the incidence of the TEAEs was derived from the latest data cut of MajesTEC-1 and LocoMMotion. TEAEs were included if they occurred in 5% of the all treated population in MajesTEC-1 and were classified as grade 3-4 TEAEs. The TEAEs included in the model are presented in Sections 7.

8.3 Extrapolation of relative efficacy

The relative effectiveness used to inform the PSM was sourced from clinical studies MajesTEC-1 and LocoMMotion, [25] [75] for teclistamab and physician's choice, respectively. Additional sources include Danish life tables for background mortality [90]. Time to event data from the studies were extrapolated over the time horizon of the analysis. Background mortality was incorporated in the long-term extrapolations of events to avoid predicted hazards below competing hazards for the general Danish population. The following section includes details of the extrapolation of relative effectiveness used in the cost effectiveness analysis.

8.3.1 Time to event data – overview

[redacted].

[redacted]

[redacted]

[redacted]

8.3.2 Progression free survival

[redacted]

Figure 27. Kaplan-Meier estimates for PFS in the ITT population from MajesTEC-1 (teclistamab) and LocoMMotion (physician's choice)


[redacted]

Abbreviations: ATT=Average treatment effect in the treated population.

[redacted]

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Figure 28. Log cumulative hazard and Schoenfeld residuals for progression free survival for teclistamab

[redacted]

[redacted]

8.3.2.1 Goodness-of-fit statistics

[redacted]

Table 32. Goodness-of-fit statistics for the different survival models for progression free survival for teclistamab

	Teclistamb		Physician's choice		Total ΔAIC_{min}	Total ΔBIC_{min}
	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}	ΔBIC_{min}		
[redacted]						

Abbreviations: AIC=Akaike information criterion, BIC=Bayesian information criteria.

8.3.2.2 Visual fit

[redacted]

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Figure 29. All models overlayed on the Kaplan-Meier estimate for progression free survival in the teclistamab arm.

Figure 30. All distributions for progression free survival in the teclistamab arm, long-term projection

Abbreviations: PFS=Progression free survival, KME=Kaplan-Meier estimate

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Figure 31. All models overlayed on the Kaplan-Meier estimate for progression free survival in the PC arm

Figure 32. All distributions for progression free survival in the PC arm, long-term projection

Abbreviations: PFS=Progression free survival

8.3.2.3 Extrapolated event rates

Table 33. Proportion of patients progression free alive at landmark survival times for teclistamab and physician's choice

Extrapolation distribution	Treatment arm	Mean survival (months)	Mediansurvival (months)	6 months	18 months	24 months	48 months	60 months	Δmean

[redacted]

8.3.2.4 Conclusion of progression-free survival

[redacted]

Figure 33. Base case progression free survival (PFS) extrapolations; teclistamab: lognormal; PC: lognormal

[redacted]

Abbreviations: PFS=Progression free survival, KM=Kaplan-Meier, TEC=teclistamab, PC=Physician's choice

8.3.3 Overall survival

[redacted]

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Figure 34. Kaplan-Meier estimates for OS in ITT population from MajestTEC-1 (teclistamab) and LocoMMotion (Physician's choice)

Diagnostic plots (log cumulative hazards, and Schoenfeld residuals) together are presented in Figure 35.

Figure 35. Diagnostic plots for overall survival for teclistamab and physician's choice

[redacted]

8.3.3.1 Goodness-of-fit statistics

[redacted]

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[redacted]

Table 34. Goodness-of-fit statistics for the different survival models for OS for teclistamab

	Teclistamb		Physician's choice		Total ΔAIC_{min}	Total ΔBIC_{min}
	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}	ΔBIC_{min}		
[redacted]						

Abbreviations: AIC=Akaike information criterion, BIC=Bayesian information criteria

8.3.3.2 Visual fit

[redacted]

Figure 36. The best fitting distributions overlayed on the Kaplan-Meier estimate for overall survival in the teclistamab arm

[redacted]

Abbreviations: OS=Overall survival, KME=Kaplan-Meier estimate

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Figure 37. The best fitting distribution for overall survival in the teclistamab arm, long-term projections

Abbreviations: OS=Overall survival

[redacted].

Figure 38. The best fitting distributions overlayed on the Kaplan-Meier estimate for overall survival in the physician's choice arm

Abbreviations: OS=Overall survival, KME=Kaplan-Meier estimate

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Figure 39. The best fitting distribution for overall survival in the physician's choice arm, long-term projections

Abbreviations: OS=Overall survival

8.3.3.3 Development of the hazard of death

Figure 40. Hazard of death for all survival model distributions for teclistamab, MajesTEC-1

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Figure 41. Hazard of death for all standard survival model distributions for physician's choice, LocoMMotion

8.3.3.4 Extrapolated event rates

[redacted]

Table 35. Proportion of patients alive at landmark survival times for teclistamab and physician's choice

Extrapolation distribution	Treatment arm	Mean survival (months)	Median survival (months)	6 months	12 months	24 months	48 months	60 months	Δmean
[redacted]									
[redacted]									
[redacted]									

8.3.3.5 Conclusion of overall survival extrapolations

[redacted]

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Figure 42. Base case overall survival (OS) extrapolations; teclistamab: lognormal; PC: lognormal

Abbreviations: OS=Overall survival, KM=Kaplan-Meier

8.3.3.6 Summary of the chosen parametric functions

Table 36. Summary table of the chosen parametric functions

Endpoint	Arm	Distribution	Section
PFS	Teclistamab	Lognormal	Section 8.3.2
	Physician's choice	Lognormal	Section 8.3.2
OS	Teclistamab	Lognormal	Section 8.3.3
	Physician's choice	Lognormal	Section 8.3.3
TTD	Teclistamab	Lognormal	Section Appendix G Extrapolation
	Physician's choice	Lognormal	Section Appendix G Extrapolation
AFS	Teclistamab	Gompertz	Section Appendix G Extrapolation

Abbreviations: OS = Overall survival, PFS = Progression free survival, TTD = Time to discontinuation, AFS = Administration Frequency Switch.

8.3.3.7 Clinical plausibility

1. [redacted]

[redacted]

Table 37. Undiscounted life years using the base case progression-free survival (PFS) distribution (lognormal)

Lognormal PFS	Teclistamb (life years)		Physician's choice (life years)		Incremental difference (life years)		
[redacted]							

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

The model used health state dependent utilities. In the progression-free (PF) state, either time-dependent utility or an overall PF state utility can be applied. A single PPS utility value was assigned to all patients in the post-progression health state. Utility estimates were derived from the MajesTEC-1 trial. AE-related utility decrements were calculated for a specified duration and applied as a one-off upon the start of the PF state. The model contains an option to use either a treatment-related disutility or disutilities associated with each AE. In the MajesTEC-1 clinical trial, patients in the Phase 2 part of the study 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) [97].

Utility for the PF state was obtained from analysis of MajesTEC-1 EQ-5D-5L data, consistent with the preferred measure of HRQoL by the Danish Medicine Agency [98].

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.

EQ-5D-5L utility scores were derived using preference weights based on the general Danish population [99] according to DMC methods guide [98].

The health state utility values used in cost effectiveness analysis are summarized in Table 38, Table 39 and Table 41 below.

8.4.1.1 Progression free health state utility values

In order to capture the impact of increasing utility estimates in the PF state on QALY outcomes, the model base case applied time-dependent utilities to patients in PF state. Time-dependent utilities may be estimated using a single

MMRM, that includes all pre-progression utility estimates from all patients. One drawback of this method 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 plotted in Figure 43 and provided in Table 38.
The increasing utility values are in line with the patient heterogeneity assumption mentioned in section 61. More specifically, it is assumed that patients in a worse health state will have progressed before the patients who are in a better health state and subsequently who also have better response to treatment. This implies that at every time point for which utility values are measured, the patient population has better health outcomes. Hence, it is reasonable to assume that the utilities will increase over time.

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.

The model linearly interpolates utility values in Table 38 to obtain model cycle specific utilities. The latest time-dependent utility estimate (0.890 in Table 38) was then carried forward.

Figure 43. Time dependent mean pre-progression utility values

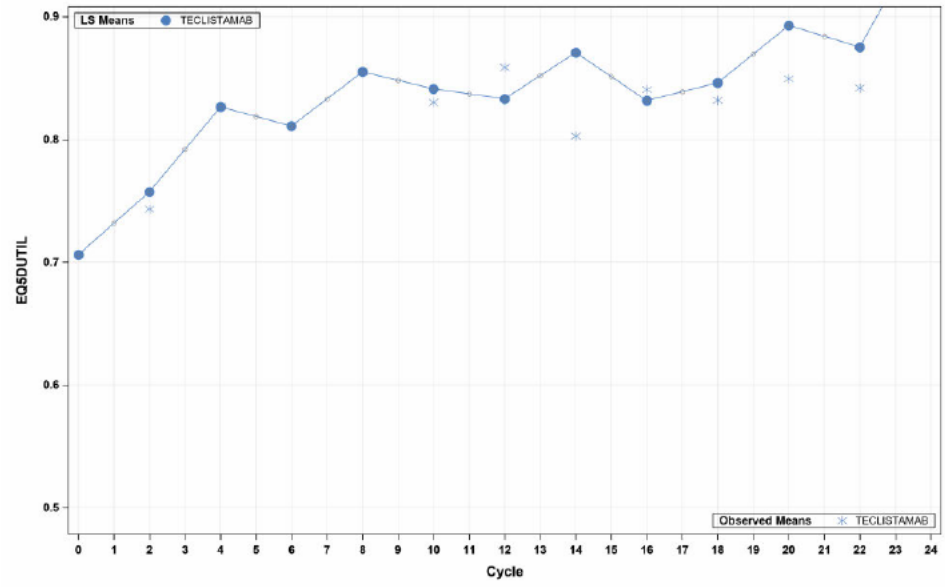

Table 38. Time-dependent utilities in pre-progression state (based on mixed model for repeated measures [MMRM])

Time (days)	Time (28 days)	n	Mean	SE	Lower 95% CI	Upper 95% CI
0	0	96	0.7062	0.0310	0.6455	0.7669
56	2	80	0.7574	0.0324	0.6938	0.8210

112	4	66	0.8265	0.0326	0.7627	0.8903
168	6	64	0.8110	0.0336	0.7451	0.8769
224	8	61	0.8551	0.0332	0.7900	0.9202
280	10	56	0.8412	0.0368	0.7690	0.9134
336	12	50	0.8331	0.0399	0.7549	0.9113
392	14	46	0.8708	0.0433	0.7859	0.9557
448	16	44	0.8317	0.0413	0.7508	0.9126
504	18	41	0.8462	0.0436	0.7608	0.9316
560	20	35	0.8928	0.0393	0.8157	0.9699
616	22	34	0.8753	0.0417	0.7936	0.9570
672	24	28	0.9792*	0.0538*	0.8738*	1.0846*

Abbreviations: PF = progression free; SE = standard error
* The latest cycle estimate is based on a small number of patients, in the health economic model the cycle 24 PF utility was assumed to be equal to the previous cycle estimate (0.8753).
Source: [25].

8.4.1.2 Progressed health state utility value

The utility value of 0.740 for the post progression survival (PPS) was derived from MajestTEC-1 (see Table 39).

Table 39. 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

Source: [25].

8.4.1.3 Age adjusted health state utility values

Age adjustment for health state utility values (HSUV) was implemented in the base case analysis according to the DMC guidelines [98]. When calculating the HSUV over time, the multiplicative method was used. The DMC has provided Danish standard values [98] which were used to calculate an index which was be applied to the QALYs over time. 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 40. Danish general population utility values stratified by age groups

Age group	Utility values
0-17	1
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

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8.4.1.3.1.1 Caregiver disutility

The effect on the HRQoL of caregivers was not included in the cost-effectiveness analysis, because there was no documented evidence identified that showed changes in HRQoL of caregivers for neither teclistamab nor physician's choice.

8.4.1.3.2 Adverse Event disutilities

Utility decrements for adverse events were used in the base case; the exclusion of these disutilities was tested in a scenario analysis. Utility decrements due to AEs were sourced from publications and previous HTA submissions. The duration of utility decrements was based on MajesTEC-1 [25]. All inputs and sources are presented in Table 41.

Table 41. Summary of adverse event disutilities applied in the model

Adverse event	QALY decrement	Decrement Source	Duration of AE (Days)	Duration Source	AE-related utility decrement
Anemia	-0.3100	[100]	9.51	MajesTEC-1	**-0.0081**
CRS, Grade 1-2	-0.1109	CARTITUDE-1	3.25	MajesTEC-1	**-0.0010**
CRS, Grade 3+	-0.6931	Assumed to have 0 quality of life	3.00	MajesTEC-1	**-0.0057**
Hypertension	0.0000	Hypertension was assumed to be therapeutically managed, with no impact on quality of life	4.11	MajesTEC-1	**0.0000**
Hypophosphatemia	-0.1500	Data on utility decrements for hypophosphatemia was not identified, and a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed.	9.30	MajesTEC-1	**-0.0038**
Leukopenia	-0.0700	No data found. Assume lowest in range, Brown 2013/Partial Review TA171(Bacelar 2014)[101]	14.92	MajesTEC-1	**-0.0029**
Lymphopenia	-0.0700	No data found Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014)[101]	30.80	MajesTEC-1	**-0.0059**
Neutropenia	-0.1500	[102]	31.46	MajesTEC-1	**-0.0129**
Pneumonia	-0.1900	[103]	11.62	MajesTEC-1	**-0.0060**
Thrombocytopenia	-0.3100	Assume same disutility as anemia [100]	22.80	MajesTEC-1	**-0.0194**

8.4.2 Health state utility values used in the health economics model

As described above, the weights used to calculate QALYs were measured in MajesTEC-1 using the EQ-5D-5L instrument. The utility values for the pre- and post-progression states were derived based on the Danish EQ-5D-5L value set according to Jensen et al. 2021 [9]. The Danish tariff was considered the most relevant in line with the DMC guidelines [98]. The health state utility values used in the model was age adjusted according to what was described in section 8.4.1.3, and are presented Table 38 and Table 39. The disabilities used in the model base case were the AE related and are presented above in Table 41. No disutility was applied for caregivers.

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8.5 Resource use and costs

Costs considered in the analysis include drug acquisition cost, drug administration costs, co-medication cost, subsequent treatment, routine follow-up and monitoring cost, cost of managing AEs, end of life costs and non-medical cost including patient time and travel cost. All costs are reported in DKK and were sourced from the latest available public price list from 2022 [104, 105]. The assumed resource use was verified by a Danish clinical expert [60]. The costs of treatment-specific AEs associated with teclistamab and Physician's choice were estimated based on incidence rates for AEs and per-event treatment costs and applied as one-off costs at the start of the PFS health state. The cost of subsequent treatment (costed as a market basket) was applied as a one-off cost at the start of the PPS health state.

8.5.1 Treatment costs

8.5.1.1 Cost of intervention

Patients on teclistamab were assumed to have two priming administrations (60 and 300 mcg/kg), followed by a regimen of weekly administrations (1500 mcg/kg) until disease progression (see Figure 44).

Figure 44. Teclistamab Dosing Schedule

Drug costs for teclistamab were assumed to be 6,733.03 DKK and 34,338.46 DKK for 30,000 mcg and 153,000 mcg, respectively. See Table 42 for summary of intervention price.

Table 42. Summary of intervention price

	Pack size	Strength	Price per pack (DKK)	Reference
Teclistamab (priming dose only)	1	10 mg/ml	6,733.03	Janssen Pharmaceuticals
Teclistamab	1	90 mg/ml	34,338.46	Janssen Pharmaceuticals

In the CEM, some patients move on from weekly dosing to bi-weekly dosing in accordance with the chosen extrapolation distribution for AFS. These moves are occurring successively—which is how it did occur in MajesTEC-1 and furthermore how it is expected to occur in clinical practice. No patient is switched to quarter-weekly dosing despite this being an occurrence amongst a few patients in MajesTEC-1. To not overestimate the cost of teclistamab, Q2W dosing was applied in the base case analysis—bi-weekly dosing is by Janssen not viewed as a study artefact and it is approved by EMA.

8.5.1.2 Cost of comparator

Unit drug costs for the comparators in physician's choice were based on pharmacy purchasing prices (PPP) available in the Laegemiddelstyrelsen price database [106]. The respective dosing and proportion of patients receiving each regimen are presented in Table 6 and Table 7 (Section 5.3).

For a list of the regimens received in more than four patients, in LocoMMotion, see further section 18.1.5, Table 70.

Table 43. Cost of physician's choice

Item	Type of administration	Strength	Pack size	Price per pack PPP (DKK)	Source
Bortezomib	SC	3.5 mg	1	1,940	Laegemiddelstyrelsen [106] varenummer:179371
Carfilzomib	IV	60 mg	1	8,229.46	Laegemiddelstyrelsen [106] varenummer: 534401
Dexamethasone	Oral	4 mg	100	331.20	Laegemiddelstyrelsen [106] varenummer: 579043

Pomalidomide	Oral	4 mg	21	55,580.91	Laegemiddelstyrelsen [106] varenummer: 461441

Abbreviations: IV = Intravenous, PPP = Pharmacy purchasing price.

8.5.2 Wastage

In clinical practice, wastage is expected to be avoided through vial sharing and administering treatment to several patients on the same day. This is performed to maximize the usage and minimize the cost for the drugs.

In practice, patients could be called in at the same day in order to bundle vial volumes and limit wastage as much as possible: Patient coordinators at hospitals may coordinate appointments accordingly. Hospitals could wait for patients to arrive and before arrival hospital pharmacy are requested to produce ready-to-use syringes, to avoid wastage further, in case a patient misses an appointment. Doses are prepared for each patient, marked with patient name and/or code and can be stored up to 20 hours according to SPC.

According to clinical experts with experience of treating MM in Norway, vial sharing is a common practice at clinics [107, 108] which was confirmed by the Norwegian Medicines Agency in their assessment of Tecvayli® [109]. This assumption was validated by a Danish pharmacist and clinical doctor (see section 11). According to the Danish experts, vial sharing is standard practice within the field and the logistic of coordinating the patients are already part of the way the doctors see their patient in a clinical setting (multiple patients in one day). They also assume that this practice should be possible in all treating departments in Denmark. In the base case analysis, 50% wastage was assumed both for the intervention and the comparator. This was considered to represent the expected vial sharing in clinical practice. It is not anticipated that all clinics avoid wastage this efficiently. A scenario with no wastage assumption was tested in a scenario analysis.

8.5.3 Drug administration costs

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. Cost per day amounts to 4295.73, based on DRG16MA11. Concerning physician's choice, the respective cost of drug administration was applied to each of the drug included in the regimens. The Interactive DRG by Sunhedsdatastyrelsen [110] was used to source the cost of administration. More specifically, DRG 17MA88: Diagnose (DC900) Myelomatose and procedure (BWAA31) Medicingivning ved subkutan injection and (BWAA62) Medicingivning ved intravenøs infusion, for subcutaneous and intravenous administration was used, respectively. For oral drug administration, no additional cost was assumed. A cost of 3,225 DKK respectively was assumed based on the code 17MA88. Given that IV is generally a more invasive administration form than SC this approach may be conservative in favor of IV treatment combination containing IV formulations. See Table 44 for an overview of drug administration costs.

Table 44. Drug administration costs

Input	Cost (DKK)	Comment	Source
IV infusion	3,225	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	Sundhedsdatastyrelsen Interactive DRG[110]
SC administration	3,225	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	Sundhedsdatastyrelsen Interactive DRG[110]
Oral drug administration	0	Assumption	

8.5.4 Concomitant Medication

Cost for concomitant medications are expected to have a limited effect on the outcome (ICER) and is therefore not accounted for within the analysis.

8.5.5 Subsequent Treatment Costs

Subsequent treatment impacts costs but not directly survival outcomes in the model. The cost of subsequent treatment is captured in the PPS health state and applied as a one-off cost at disease progression to a specified proportion of patients. The proportion receiving subsequent treatment was 65.8% in the teclistamab arm and 73.0% in the physician's choice arm, based on data from the respective trials, MasjesTEC-1 and LocoMMotion. Subsequent treatment cost was

applied for a specified treatment duration 5.77 months in both arms, based on Young et al (2016) [111], and with the assumption, for simplicity, that subsequent therapy was comprised of the same treatment mix used in the physician's choice basket (assumed to be the same in both treatment arms).

All assumptions around the costing of subsequent treatment are presented in Table 45. A scenario was done applying the same proportion of 65.8% receiving subsequent treatment in both arms seen in MajesTEC-1.

See Table 43 for details of the price for the subsequent treatment costs which were calculated for the regimens in the basket according to the dosing schedule in Table 7.

Table 45. Subsequent Treatment Mix

Treatment regimen	Teclistamab	Physician's choice	Source
% receiving any subsequent treatment	65.8%	73.0%	MajesTEC-1 DCO January 2023, LocoMMotion DCO October 2022
Duration of subsequent treatment (months)	5.77	5.77	Yong et al (2016) [111]
Total monthly costs (DKK)	65,736	65,736	Calculated in CEM
Treatment mix for those receiving subsequent treatment:			
Regimen	%	%	
Kd	**33.3%**	**33.3%**	LocoMMotion [75], Danish survey [59]
Pd	**33.3%**	**33.3%**	
PVd	**33.3%**	**33.3%**	

Abbreviations: Kd=Carfilzomib plus dexamethasone; Pd=Pomalidomide plus dexamethasone; PVd=Pomalidomide plus bortezomib plus dexamethasone.

8.5.6 Monitoring cost

The model captured routine monitoring costs the PFS and PPS state.
Table 46 presents the procedures and frequencies of medical resources by health state. The types and frequencies of resources were based on Danish clinical expert validation that confirmed that visits and test are done once per month [60]. Post-progression frequency of resource use was assumed the same (once per month) as in pre-progression and the weekly cost was calculated to 404.47 DKK. The unit costs for the test and visits were taken the latest available price list (Takstjort April 2022) available from Laegeforeningen [104]. See
Table 46 for individual costs for routine care items.

Table 46. Weekly resource use for routine follow-up care

Item	Pre-progression*	Post-progression	Cost (DKK)
Hematologist visit	0.25	0.25	1,527
Full blood count	0.25	0.25	21
Biochemistry	0.25	0.25	21
Protein electrophoresis	0.25	0.25	21
Urinary light chain excretion	0.25	0.25	28
Average weekly cost for resource use (DKK)	**404.47**	**404.47**	

*Source: Hematology visit; Ledende overlaeger/professor [112] Lab test; Ydelsesnummer 7110 - Takstkort 29A - Oktober 2021 [104]

8.5.7 Adverse events costs

Costs of adverse events were sourced based on conversion of the international classification of disease version 10 (ICD-10) codes to relevant Danish diagnosis related group (DRG) codes. The costs were sourced from the 2022 Diagnosis Related Group (DRG) codes - rates list available from Sundhedsdatastyrelsen [105]. Table 47 shows the costs for the AEs.

Table 47. Cost of adverse events

Adverse Events	Cost (DKK)	Comment/Source
Anemia	41,278	DRG 16MA05, DRG_Takster 2022 [105]
CRS, Grade 1-2	3,108	Assumption Fever, DRG 18MA04 divided by Trimpunkt 6, DRG_Takster 2022 [105]
CRS, Grade 3+	33,310	Assumption
Hypertension	16,630	DRG 05MA11, DRG Takster 2022 [105]
Hypophosphatemia	6,224	DRG 23MA05, DRG_takster 2022 [105]
Leukopenia	14,836	DRG 17MAO5, DRG_takster 2022 [105]
Lymphopenia	14,836	DRG 17MAO5, DRG_takster 2022 [105]
Neutropenia	18,926	DRG 49PR07, DRG_takste 2022 [105]
Pneumoniae	40,070	DRG 04MA13, DRG_Takster 2022 [105]
Thrombocytopenia	38,408	DRG 16MA03, DRG _Takster2022 [105]

Abbreviations: AST= Alanine transaminase; CRS= Cytotoxic release syndrome.

8.5.8 End of life costs

The analysis included a specific cost to reflect additional resource use associated with the end of life (Table 48). The cost was sourced from the 2022 DRG list available from Sundhedsdatastyrelsen [105].

Table 48. End of life costs

Item	Value (DKK)	Comment/Source
End of life	71,612	DRG 26MP48, Specialiseret Palliativ indsats, Øvrig, DRG_Takster 2022 [105]

8.5.9 Non-medical costs

Non-medical costs were derived for patients by estimating the time spent due to administration and visits and transportation costs (round trip). Patient costs were sourced from the Danish statistics bank (Statistics Denmark) on the basis of LONS20 and four hours per administration or visit was assumed. Transportation costs for a roundtrip were sourced from the Danish statistics bank on the basis of the state tax free driving allowance using CPI inflation to represent the cost for 2021 [113]. The costs and resource use applied in the analysis are presented in Table 49.

Table 49. Non-medical costs per health state (weekly)

Health state	Weekly visits/ Resource use	Patient time cost	Transportation cost (Roundtrip)	Average weekly patient cost (DKK)
PFS	0.25	179 DKK x 4 hours/visit	99 DKK	**203.65**
PPS	0.25	179 DKK x 4 hours/visit	99 DKK	**203.65**

8.6 Results

8.6.1 Base case overview

Table 50. Base case overview

Comparator	Standard care/Physicians' choice
Type of model	PSM
Time horizon	40 years (lifetime)
Treatment line	4th line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in MajesTEC-1. Danish population weights were used to estimate health-state utility values
Included costs	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs
Dosage of pharmaceutical	Based on BSA
Average time on treatment	Teclistamab: 31.0 months

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	Physician's choice: 5.9 months
Parametric function for PFS	Teclistamab: Lognormal Physician's choice: Lognormal
Parametric function for OS	Teclistamab: Lognormal Physician's choice: Lognormal

8.6.2 Base case results

Table 51 presents total costs, life-years gained, QALYs, and incremental costs per QALY for teclistamab versus physician's choice. Compared with physician's choice, teclistamab generated 1.93 incremental QALYs and 2.30 incremental life-years gained with a higher total cost. The incremental cost (in DKK) per QALY gained was 1,177,384. Disaggregated discounted base case results for quality-of-life outcomes and cost outcomes are presented in Table 52 and Table 53, respectively.

Table 51. Base case of the analysis

	Teclistamab	Physician's choice	Incremental
Total life years (LY)	3.98	1.79	2.19
Total quality adjusted life years (QALYs)	3.20	1.36	1.84
Total cost (DKK)	2,720,874	852,350	1,868,524
ICER (DKK)			**1,013,985**

Abbreviations: ICER = Incremental cost effectiveness ratio; LY = life years; QALYs = Quality adjusted life years.

Table 52. Disaggregated utility results (discounted)

	Teclistamab	Physician's choice	Incremental
PFS	2.37	0.51	1.85
PPS	0.86	0.86	0.00
Disutility	-0.02	-0.01	-0.02
Total QALYs	3.20	1.36	1.84

Abbreviations: PFS = Progression free survival; PPS = Post progression state; QALYs = Quality adjusted life years.

Table 53. Disaggregated cost results (discounted)

	Teclistamab	Physician's choice	Incremental
Total PFS cost	*2,537,496*	*528,807*	*2,008,688*
Total treatment costs	2,339,085	474,4180	1,864,668
Drug cost	2,085,438	407,804	1,677,634
Kd		167,465	-167,465
Pd		119,694	-119,694
PVd		120,644	-120,644
Administration cost	253,648	66,614	187,033
Kd		38,748	-38,748
Pd			-
PVd		27,866	-27,866
Follow-up cost	59,101	13,326	45,776
AE cost	51,973	17,257	34,716
Total Non medical costs	87,336	23,807	63,529
Travel costs	10,570	2,881	7.689
Kd		1,455	-1,455
Pd		304	-304
PVd		1,123	-1,123
Patient time	76,766	20,925	55,840
Kd		10,568	-10,568
Pd		2,204	-2,204
PVd		8,152	-8,152
Total PPS	*183,379*	*323,542*	*-140,163*
Follow-up cost	24,926	24,541	385
Subsequent treatment cost	80,352	211,411	-131,059
Total non-medical costs	15,159	19,220	-4,061

Travel costs	1,835	2,326	-492
Patient time	13,324	16,894	3,570
End of life cost	62,942	68,371	5,429
Total cost	**2,720,874**	**852,350**	**1,868,525**

Abbreviations: AE = Adverse event; D= Daratumumab; DVd= Daratumumab plus bortezomib plus dexamethasone; ERd= Elotuzumab plus lenalidomide plus dexamethasone; IRd= Ixazomib plus lenalidomide plus dexamethasone; Kd=Carfilzomib plus dexamethasone; KRd= Carfilzomib plus lenalidomide; PFS = Progression free state; PPS = Post progression state.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

A one-way deterministic sensitivity analysis (OWSA) was conducted. Input values were varied using the 95% confidence interval for both lower and upper bound. Uncertainty regarding the switch to bi-weekly dosing was not accounted for within the OWSA, but there are scenario analyses exploring that. Table 54 shows the results of the OWSA including the 10 values which had the largest impact on the ICER when being varied. The tornado diagram in Figure 45 shows the ten most sensitive values.

Table 54. OWSA – the 10 most influential model parameters

Parameter	Lower bound	Upper bound	Lower bound (DKK)	Upper bound (DKK)	Absolute diff. (DKK)
Base Case			1,013,985		
PFS time dependent utility - Time (28 days) - 24	0,78	0,94	1.107.609	953.236	154.373
Proportion vial sharing	0,40	0,60	1.049.194	978.775	70.419
Duration of subsequent treatment - Physician's choice	4,64	6,90	1.037.201	990.769	46.432
% taking subsequent treatment - Physician's choice	0,58	0,86	1.038.609	993.178	45.431
Unit cost - SC administration	2.623,99	3.887,06	993.749	1.036.276	42.526
Body weight (mean)	72,47	77,57	993.590	1.035.930	42.339
Age (mean)	62,43	65,37	1.002.643	1.027.235	24.593
% of Kd	0,24	0,43	1.025.263	1.001.902	23.361
% of Pd	0,24	0,43	1.004.499	1.024.147	19.648
Duration of subsequent treatment - Teclistamab	4,64	6,90	1.005.161	1.022.809	17.647

Abbreviations: Pd = Pomalidomide and dexamethasone; PPS=post progression survival; PFS=progression-free survival; SC = Subcutaneous.

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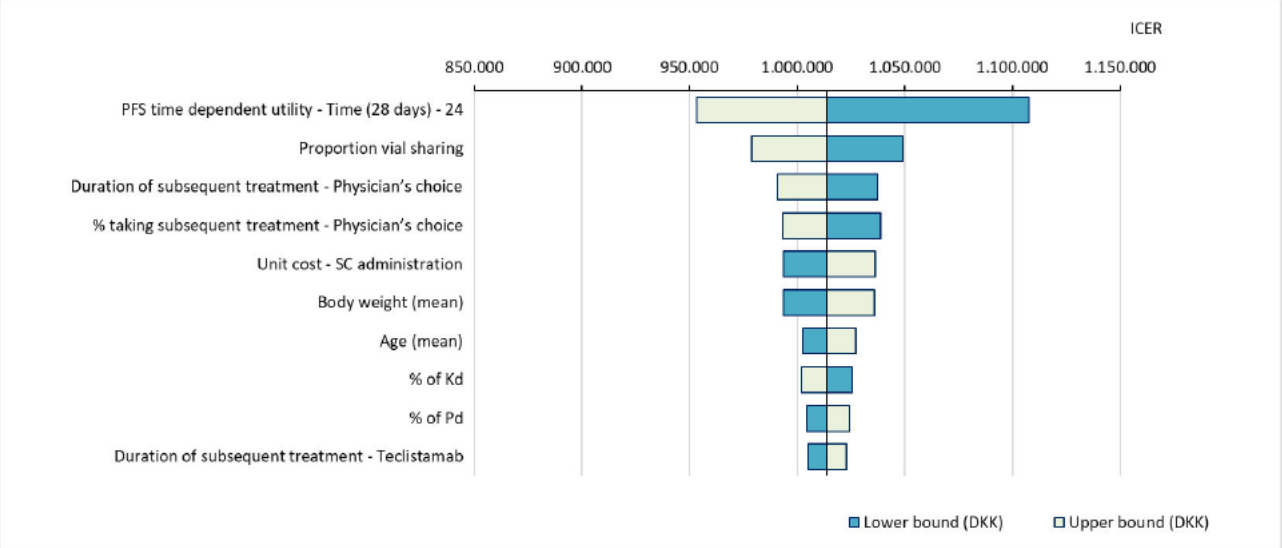
Figure 45. Tornado diagram



Abbreviations: PCd = Pomalidomide plus carfilzomib and dexamethasone; Pd = Pomalidomide and dexamethasone; PPS=post progression survival; PFS=progression-free survival; SC = Subcutaneous; VCd = bortezomib plus cyclophosphamide and dexamethasone; Vd = bortezomib and dexamethasone.

The OWSA showed that the ICER was most sensitive to total number of patients switching, the utility for PFS at 28 days and the proportion of vial sharing. The number of patients switching from weekly to biweekly dosing directly impacts the cost of teclistamab so it is natural that it has a large impact on the outcome of the analysis.

8.7.2 Scenario analysis

Scenario analyses for key model inputs are presented in Table 55.

Table 55. Scenario analyses

Parameter	Base case	Scenario	ICER (DKK)
Base case	-	-	**1,013,985**
Starting age	63.9	70	1,076,967
Distribution Teclistamab & PC OS and PFS	Teclistamab: Lognormal PC: Lognormal	Teclistamab: Loglogistic PC: Loglogistic	1,074,530
		Teclistamab: Generalized gamma PC: Generalized gamma	884,241
Distribution AFS	Gompertz	Weibull	1,014,937
		Generalised Gamma	1,015,815
		Exponential	1,017,547
		Loglogistic	1,131,488
Time horizon	40	5 years	**1,874,723**
		10 years	**1,300,801**
		15 years	**1,128,003**
		20 years	**1,056,616**
		25 years	**1,022,779**
Drug wastage	Yes	No	833,056
Vial sharing	50%	0%	1,194,914
Discount rates	Costs and benefits: 3.5% for 1-35 years, 2.5% for >36 years	Costs 0%, Benefits 0%	**888,269**
		Costs 5%, Benefits 5%	**1,070,180**
		Costs 3.5%/2.5%, Benefits 0%	**738,056**

EQ-5D-5L tariffs	Danish	UK	1,121,800
Age adjusted utilities	Yes	No	991,337
AE associated disutilities	Yes	No	1,005,442
Caregiver costs and time use	DKK 0 and 0 hours	DKK 179 and 4 hours	1,042,350

8.7.3 Probabilistic sensitivity analyses

To evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses (PSA) were conducted. The PSA included all relevant model parameters; estimates of uncertainty were based on the uncertainty in the source data where data availability permitted. Variance data were not available for all parameters and for those parameters a variance of 10% from the mean was applied. Table 78 in Appendix J Probabilistic sensitivity analyses, presents the parameters included in the PSA as well as the standard error and selected probability distributions.

A second-order Monte Carlo simulation was run for 1,000 iterations including the simultaneous variation of all parameters. Multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values. Figure 46 presents the cost-effectiveness plane, which showed that all of the 1,000 iterations were in the North-East quadrant. This means that teclistamab resulted in more QALYs and higher costs compared to physician's choice.

Figure 46. Cost-effectiveness plane

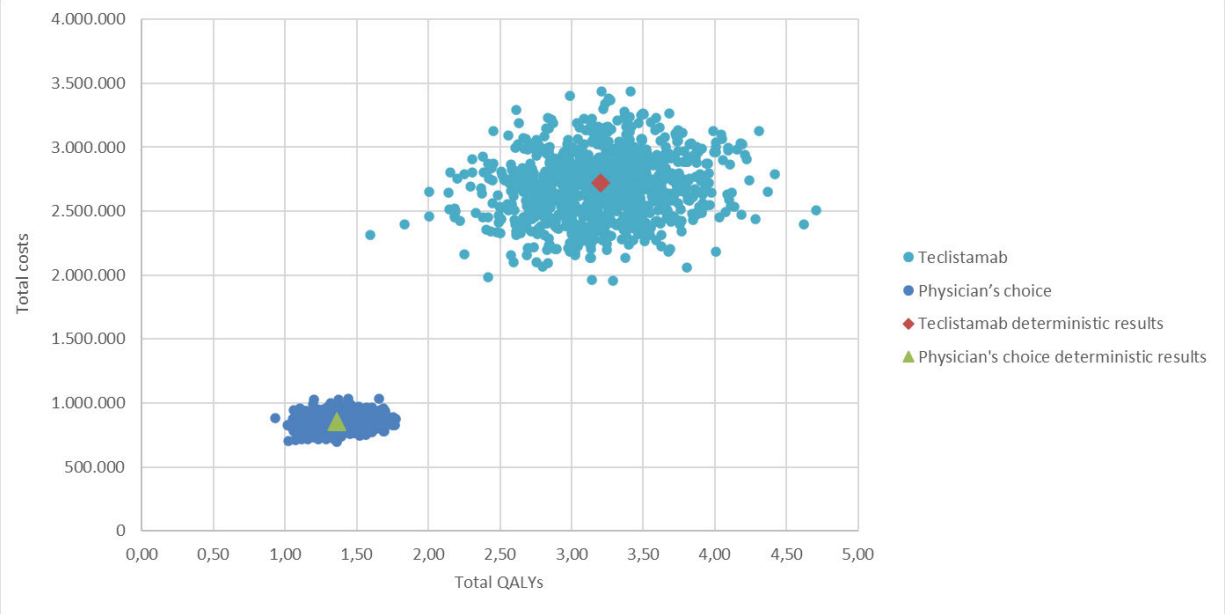
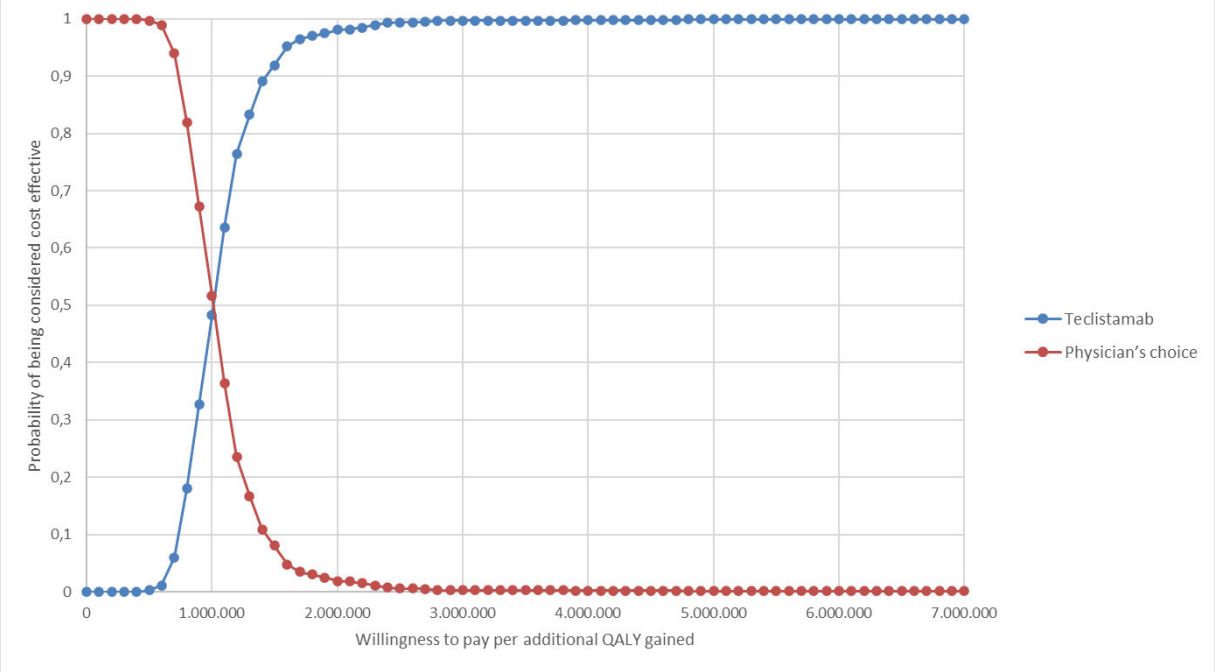


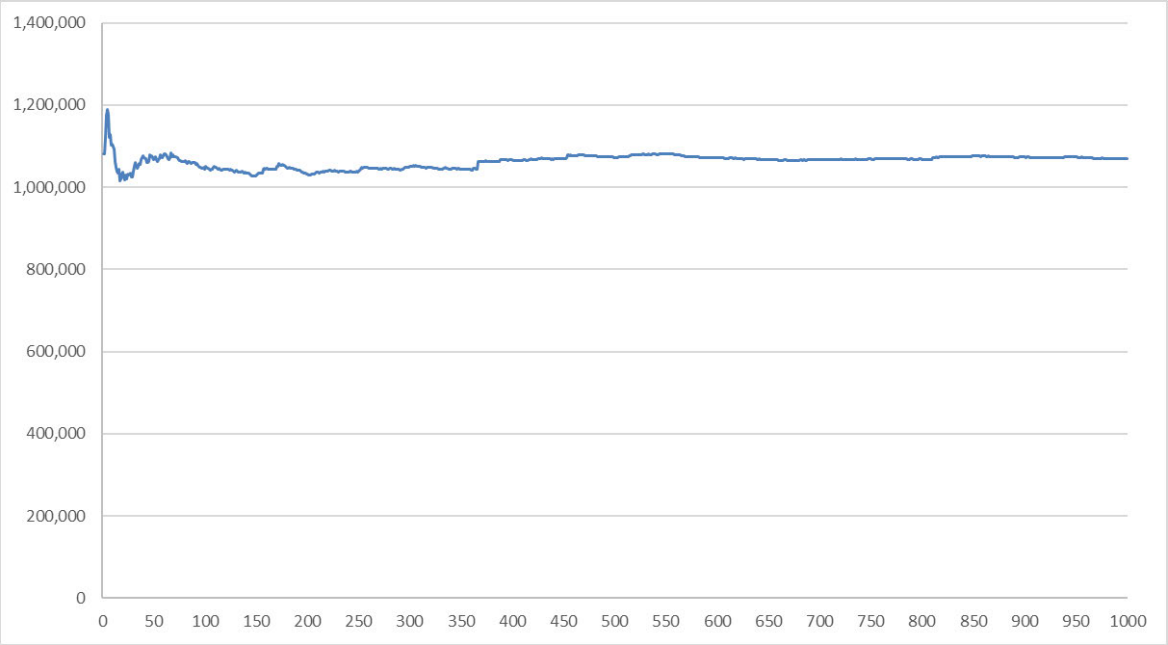
Figure 47 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that teclistamab's probability of being cost-effective is approximately 50% at a willingness-to-pay of 750,000 DKK.

Figure 47. Cost-effectiveness acceptability curve



The PSA was performed using 1,000 iterations which was deemed to be sufficient given the limited variation beyond 350-400 iterations as can be seen in the convergence plot in Figure 48 below.

Figure 48 Convergence plot for the estimated mean



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9. Budget impact analysis

9.1 Number of patients

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 teclistamab per year. A constant rate was assumed over the five-year period of 70 new patients per year. The numbers presented in Table 56 and Table 57 represent the number of patients expected to be treated in a scenario when teclistamab is introduced and one scenario when teclistamab is not introduced. For full details on the market share for the specific PC regimens, please refer to the BIM_Inputs sheet in the CEM model.

Table 56. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	2023	2024	2025	2026	2027
Teclistamab	11	18	21	28	28
Physician's choice	59	52	49	42	42
Total number of patients	70	70	70	70	70

Table 57. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	2023	2024	2025	2026	2027
Teclistamab	0	0	0	0	0
Physician's choice	70	70	70	70	70
Total number of patients	70	70	70	70	70

9.2 Budget impact

An estimation of the budget impact of introducing teclistamab in Denmark is shown in Table 58.

Table 58 Expected budget impact of recommending the pharmaceutical for the current indication

	2023	2024	2025	2026	2027
The pharmaceutical under consideration is recommended (total cost)	**51,403,589**	**64,879,716**	**73,090,258**	**81,705,871**	**87,335,035**
Of which: Drug costs	29,703,410	39,778,782	46,461,623	54,219,490	58,971,672
Of which: Administration cost	4,747,776	5,973,648	6,736,805	7,636,090	8,136,818
Of which: Follow up cost PFS	735,757	973,520	1,142,508	1,305,580	1,454,312
Of which: Follow up cost PPS	411,062	773,875	1,000,503	1,138,042	1,244,522
Of which: Subsequent treatment	11,897,306	12,165,064	11,949,202	11,157,201	11,135,004
Of which: Adverse reaction costs	1,572,520	1,815,531	1,937,037	2,180,048	2,180,048
Of which: End of life	2,335,758	3,399,296	3,862,580	4,069,420	4,212,659
Minus: The pharmaceutical under consideration is NOT recommended	**45,893,654**	**52,430,994**	**54,654,984**	**55,685,439**	**56,249,160**
Of which: Drug costs	23,913,619	27,061,963	28,005,872	28,387,098	28,569,271
Of which: Administration cost	4,027,363	4,459,280	4,588,825	4,641,145	4,666,147
Of which: Follow up cost PFS	689,881	831,115	884,524	910,118	924,142
Of which: Follow up cost PPS					

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	448,235	864,538	1,133,763	1,314,793	1,442,159
Of which: Subsequent treatment	13,178,007	14,397,682	14,685,414	14,786,837	14,831,028
Of which: Adverse reaction costs	1,208,003	1,208,003	1,208,003	1,208,003	1,208,003
Of which: End of life	2,428,546	3,608,415	4,148,583	4,437,446	4,608,410
Budget impact of the recommendation	**5,509,935**	**12,448,722**	**18,435,274**	**26,020,432**	**31,085,875**

10. Discussion on the submitted documentation

This application reports on the comparative effectiveness, cost-effectiveness, and budget impact of teclistamab versus physician's choice for the treatment of patients with triple exposed RRMM in Denmark. The cost-effectiveness analysis predicts that in real-world use, compared with physician's choice, teclistamab may extend median survival by 2.30 years (3.87 vs. 1.57 years) and result in 1.93 additional discounted QALYs over a lifetime horizon (3.14 vs 1.20 QALYs). The majority of these gains were made pre-progression. The incremental costs of teclistamab were 2,275, 527 DKK with drug acquisition costs of teclistamab being the main cost driver. The cost per QALY gained was 1,177,384 DKK. Sensitivity analyses showed the robustness of the results against changes in model parameters and alternative assumptions.

The number of patients switching dose from weekly to bi-weekly was identified as having the largest effect on the ICER. This can be explained by the direct effect on the cost of teclistamab. Scenario analyses indicated that results were stable with the use of most alternative assumptions, the use of shorter time horizons increased the ICER, the absence of wastage and the use of alternative parametric survival curves.

Deterministic, probabilistic and scenario analyses confirmed the results of the base case analysis, and showed the results were relatively stable with regard to changes in inputs and assumptions.

The study is also subject to uncertainties and limitations. The extrapolation of short-term results over a lifetime horizon inherently introduces uncertainty into the results. Long-term survival outcomes with teclistamab are subject to uncertainty considering the relatively low event rate (49.09% censored for OS) and the lack of long-term clinical experience with teclistamab. The survival estimates derived from the best fitting distributions were optimistic, suggesting a distribution with a "fat tail" with expected long-term survivors, supported by the Gompertz distribution.

Patients enrolled in MajesTEC-1 had failed multiple prior therapies and a placebo control arm would have been deemed unethical given their poor prognosis. The LocoMMotion study was used for the analysis of physician's choice effectiveness, providing prospective OS and PFS data for physician's choice in the triple-class exposed setting. In order to estimate relative effectiveness an adjusted comparison was done, adjusting the LocoMMotion cohort to fit the trial population characteristics of MajesTEC-1.

As in any non-randomized study, the potential for residual confounding cannot be excluded. However, the availability of IPD from both cohorts enabled adjustment for imbalances in important prognostic factors. To ensure that the most important clinical factors were balanced between the two populations, an evidence-informed process was used to select the covariates for adjustment. This process considered the prognostic strength of potential covariates between MajesTEC-1 and the physician's choice cohort.

Teclistamab for the treatment of triple exposed RRMM has shown progression and survival benefits over physician's choice based on indirect comparisons between prospective clinical data. This cost-effectiveness analysis may be used to aid the decision problem of introducing teclistamab as a new standard treatment for triple-class exposed patients with RRMM in Denmark.

11. List of experts

[redacted]

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Version log

Version	Date	Change
1.0	11 November 2022	Application submitted
1.1	June 2023	Application updated with additional data from later data cuts. Data from the MajesTEC-1 January 2023 and LocoMMotion October 2022 data cuts have been included to enhance the quality of the submission.

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13. Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Janssen would like to emphasize that in our view there is no doubt that LocoMMotion is the most relevant source to estimate the efficacy of standard of care, because of its prospective trial design as well as having similar eligibility criteria as MajesTEC-1; a prospective trial design should be deemed preferable to a retrospective. However, Janssen has carried out a systematic literature review (SLR) with the following objective:

- The objective of this study was to conduct systematic literature reviews (SLRs) of clinical, health-related quality of life (HRQoL), and economic evidence investigating therapeutic regimens in patients with RRMM to support health economics and outcomes research (HEOR) and market access activities for the novel CAR-T therapy cilta-cel. The clinical SLR focused on the triple-class exposed population, while the economic and HRQoL looked at RRMM overall given the limited literature for triple-class exposed patients for these topics.

The full SLR report has been supplied to the Danish Medicines Council as part of the submission.

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14. Appendix B Main characteristics of included studies

Table 59. Main characteristics of the MajesTEC-1 study

Trial name: MajesTEC-1	NCT03145181 (Phase 1) NCT04557098 (Phase 2)
Objective	Part 1 (Dose Escalation): To identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab Part 2 (Dose Expansion): To characterize the safety and tolerability of teclistamab at the proposed RP2D(s) Part 3 (Phase 2): To evaluate the efficacy of teclistamab at RP2D
Publications – title, author, journal, year	1. Translational Modeling Predicts Efficacious Therapeutic Dosing Range of Teclistamab for Multiple Myeloma. Girgis et al. Target Oncol. 2022 2. Teclistamab in Relapsed or Refractory Multiple Myeloma. Moreau et al. N Eng J Med. 2022 3. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Usmani et al. Lancet. 2021 4. Teclistamab is an active T cell-redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma. Pillarisetti et al. Blood Adv. 2020
Study type and design	Phase 1/2, single-arm, open label, multicentre study (ongoing)
Sample size (n)	All-Treated Analysis Set (Phase 1+2 Cohort A): N = 165
Main inclusion and exclusion criteria	**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] **Exclusion criteria:** • Plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome, or primary amyloid light-chain amyloidosis • 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

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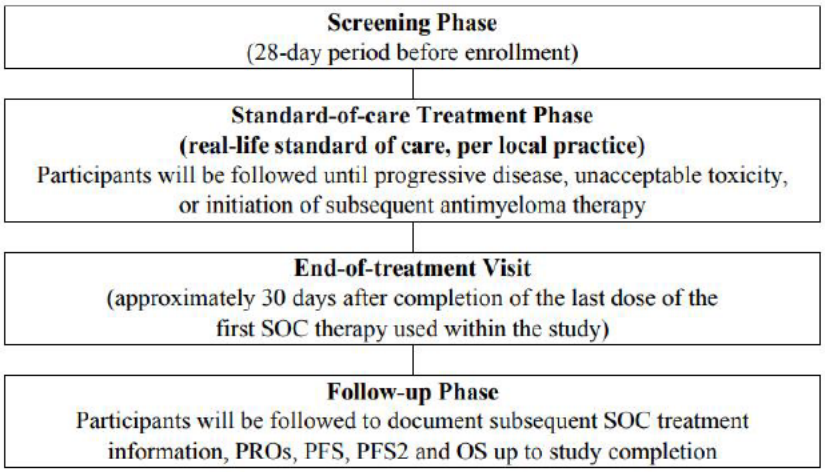
	• Certain medical conditions
Intervention	Teclistamab (Teclistamab) Dose: 1.5mg/kg, subcutaneously Dosing schedule: Step-up doses of 0.06 and 0.3 mg/kg were administered, followed by 1.5 mg/kg. The step-up doses were separated by 2 to 4 days and were completed 2 to 4 days before the administration of the first full teclistamab dose (1.5 mg/kg) Number of patients receiving the intervention: 165 patients Number of patients switching to Q2W doing: 63 Timing of switch to Q2W dosing: 11.3 months
Comparator(s)	N/A
Follow-up time	Cohort A: Median duration of follow-up: 14.1 month (range, 0.3 to 24.4), (data cut-off 16 March 2022)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint:** • ORR (PR or better) as defined by the IMWG criteria **Secondary endpoint:** • DOR • VGPR or better/CR or better/sCR as defined by the IMWG response criteria • TTR • PFS • OS • MRD negativity status • Occurrence and severity of adverse events, serious adverse events, and laboratory values • Pharmacokinetic parameters • Presence and activity of anti-teclistamab antibodies • Change from baseline in overall HRQoL, symptoms, and functioning • ORR in patients with high-risk molecular features **Exploratory endpoint:** • To explore the relationships between pharmacokinetics, pharmacodynamics, adverse event profile, and clinical activity of teclistamab • To investigate predictive biomarkers of response or resistance to teclistamab • To investigate pharmacodynamic markers • To investigate immunoregulatory activity of teclistamab • To evaluate MRU • To assess TTNT **Endpoints included in this application:** The primary endpoint was overall response rate, defined as the proportion of patients who achieve PR or better according to IMWG criteria, as assessed by the independent review committee. Secondary endpoints were time to response, duration of response, PFS and OS. Other endpoints above-mentioned were endpoints in the study, but results are not included in this application.
Method of analysis	Intention-to-treat
Subgroup analyses	Subgroup analyses are not presented in this application
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: ADC = antibody drug conjugate; BCMA = B-cell maturation antigen; CBR=clinical benefit rate; CNS = central nervous system; CR = Complete response; DLT=dose-limiting toxicity; DOR=duration of response; ECOG = Eastern Cooperative Oncology Group; ImiD = immunomodulatory drug; IMWG = International Myeloma Working Group; mAb = monoclonal antibody; MRD=minimal residual disease; MM = multiple myeloma; M protein = monoclonal paraprotein; N/A = Not applicable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PI = proteasome inhibitor; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; PR = Partial response; RO=receptor occupancy; RP2D=recommended Phase 2 dose; RRMM = relapsed/refractory MM; sCR=stringent complete response; TTR=time to response; VGPR=very good partial response.

Source: Janssen [65]

Table 60. Main characteristics of the LocoMMotion study

Trial name: LocoMMotion	NCT04035226
Objective	Primary objective: To evaluate the ORR of real-life SOC treatments in participants with RRMM. Secondary objectives: • To further evaluate the clinical benefit of real-life SOC treatments in participants with RRMM. • To evaluate PROs in participants with RRMM receiving real-life SOC treatments including disease-related symptoms, functioning, and well-being. • To evaluate the safety of real-life SOC treatments in participants with RRMM.
Publications – title, author, journal, year	1. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Mateos et al. Leukemia. 2022 2. A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving≥ 3 prior lines of therapy. Mateos et al. Wolters Kluwer Health. 2021 3. A Prospective, Non-Interventional, Multinational Study of Real-Life Current Standards of Care in Patients With Relapsed/Refractory Multiple Myeloma Who Received≥ 3 Prior Lines of Therapy. Moreau, P et al. Blood, 138: p. 3057. 2021
Study type and design	Prospective, non-interventional, multinational study (ongoing). The study design of LocoMMotion included a screening phase, a SOC treatment phase, and a follow-up phase up to 24 months from Day 1, Cycle 1 of the first treatment used. The follow-up phase continued until the end of the study. SoC are those treatments used in local clinical practice for the treatment of adult patients with RRMM. The duration of a patient's participation in this study will be at least 24 months. **Figure 49. LocoMMotion trial design** 
Sample size (n)	All Treated Analysis Set n=248
Main inclusion and exclusion criteria	**Inclusion criteria:** • Had a documented diagnosis of multiple myeloma according to IMWG diagnostic criteria. • Had measurable disease at screening (serum monoclonal paraprotein [M-protein] level ³1.0 g/dL or urine M-protein level ³200 mg/24 hours); or light chain multiple myeloma without measurable disease in the serum or the urine (ie, serum immunoglobulin free-light chain ³10 mg/dL and abnormal serum immunoglobulin kappa lambda free-light chain ratio). • Had received at least 3 prior lines of therapy or were double-refractory to a PI and an ImiD (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single regimen). Participants had undergone at least 1 complete cycle of treatment for each regimen (unless progressive disease was the best response). • Had received as part of previous therapy a PI, an ImiD, and an CD38 mAb (prior exposure can be from different monotherapy or combination regimens).

	• Must had documented evidence of progressive disease based on study physician's determination of response by the IMWG response criteria on or after the last regimen. Participants with documented evidence of progressive disease within the previous 6 months and were refractory or nonresponsive to their most recent line of treatment afterwards were also eligible. • Had an ECOG Performance Status grade of 0 or 1. **Exclusion criteria:** • No exclusion criteria due to the observational nature of the study
Intervention	SOC treatment
Comparator(s)	N/A
Follow-up time	Median duration of follow-up: 16.13 months (data cut-off 02 November 2021)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint:** • ORR (PR or better) as defined by the IMWG criteria **Secondary endpoint:** • sCR • CR • VGPR • PR • DOR • PFS • OS • PROs • TEAEs (safety) **Endpoints included in this application:** The endpoint included in this application were ORR, PFS and OS. Other endpoints above-mentioned were endpoints in the study, but results are not included in this application.
Method of analysis	NA
Subgroup analyses	Subgroup analyses are not presented in this application
Other relevant information	N/A

Note: [a] Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above.
Abbreviations: CBR Clinical benefit rate; AE= Adverse event; CR = Complete response; DOR = Duration of response; ECOG = Eastern Cooperative Oncology Group; ImiD = immunomodulatory drug; IMWG = International Myeloma Working Group; mAb = monoclonal antibody; OS = Overall survival; PFS = Progression-free survival; PR = Partial response; PI = proteasome inhibitor; PROs = Patient-reported outcomes; sCR = Stringent complete response; SAE = serious adverse event; SOC = Standard of care; RRMM = relapsed/refractory multiple myeloma; TEAE = Treatment emergent adverse events; VGPR = Very good partial response.
Sources: [114] [115].

14.1 Ongoing studies Teclistamab

Table 61 presents ongoing studies evaluating teclistamab in patients with RRMM.

Table 61. Ongoing studies in patients with RRMM

Trial name, study design and NCT number	Patient population	Treatment(s) N	Study endpoints	Status[a]
MajesTEC-3 **Randomized Phase 3** **NCT05083169**	Patients aged ≥18 years with MM according to IMWG diagnostic criteria and measurable disease at screening who have received 1-3 prior LOT including a PI and lenalidomide (participants with only 1 prior LOT must be lenalidomide refractory), documented evidence of PD, ECOG performance status grade of 0,1 or 2, and clinical laboratory values within specified range. 140 study locations in the US, Argentina, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Italy, Republic of Korea, Netherlands, Russia Federation, Spain, Sweden, Taiwan, Ukraine, and UK	Teclistamab-D, DPd, DVd N planned = 560	Primary: PFS Secondary: ORR, ≥VGPR, ≥CR, MRD-negativity, PFS on next line of therapy, OS, TTNT, AEs by severity, serum concentration of tec, ADAs to tec and D, time to worsening symptoms, change from baseline in symptoms, functioning, and overall HRQoL as assessed by EORTC QLQ-C30, MySlm-Q, PROMIS PF 8c, PRO-CTCAE, EQ-5D-5L, PGI-S, PFS and depth of response in participants with high-risk molecular features	Recruiting
Combination talquetamab and teclistamab **Open label** **Phase 1** **NCT04586426**	Patients aged ≥18 years with MM according to IMWG diagnostic criteria based on documented medical history who could not tolerate or has disease that is relapsed or refractory to established therapies, including last LOT, and ECOG performance status grade of 0 or 1. Tal+teclistamab: prior LOT must include a PI, an IMiD, and an anti-CD38 mAb. D+Tal+teclistamab: prior LOT must include a PI and an IMiD. Treatment with an anti-CD38 mAb is allowed ≥90 days prior to the study treatment if the participant did not discontinue prior treatment due to AE related to anti-CD38 therapy. Study locations in Canada, Israel, Republic of Korea, and Spain.	Tal+ teclistamab, D+Tal +teclistamab, N planned = 56	Primary: DLT and severity of DLT assessed by NCI-CTCAE (Part 1 only); AE and SAE incidence/severity (Part 2 only) Secondary: serum concentrations of tal, teclistamab, and D, anti-drug antibodies to tal, teclistamab, and D, ORR, VGPR, CR, sCR, DOR, TTR	Recruiting
Teclistamab combination therapy **Open label** **Phase 1** **NCT04722146**	Patients aged ≥18 years with MM according to IMWG diagnostic criteria and measurable disease at screening. Teclistamab + DP regimen: participant has RRMM and has received 1-3 prior LOT, including exposure to a PI and R. Teclistamab + DRV regimen: participant has newly diagnosed MM or RRMM and is naïve to treatment with R. Teclistamab-nirogacestat regimen: participant has RRMM and received ≥3 prior LOT or is double refractory to a PI and an IMiD and triple exposed to a PI, IMiD, and CD38 mAb Teclistamab + R regimen: participant has MM and has received ≥2 prior LOT,	Teclistamab + DP, Teclistamab + DRV, Teclistamab +nirogacestat, Teclistamab + R, Teclistamab + DR N planned = 140	Primary: AEs incidence & severity, abnormalities in laboratory values, DLT Secondary: ORR, VGPR, CR, sCR, DOR, TTR, serum concentrations of teclistamab, d, and nirogacestat, anti-drug antibodies to tec, d, and rHuPH20	Recruiting

	including exposure to a PI, an IMiD, and an anti-CD38 mAb Teclisramab + DR regimen: participant has MM and has received 1-3 prior LOT, including exposure to a PI and an IMiD 29 study locations in the US, Australia, Belgium, France, and UK			
Daratumumab regimens in combination with bispecific T cell redirection antibodies **Open label** **Phase 1b** **NCT04108195**	Patients aged ≥18 years with MM according to IMWG diagnostic criteria and measurable disease at screening. Must have either received ≥3 prior LOT including a PI (≥2 cycles or 2 mo of treatment) and an IMiD (≥2 cycles or 2 mo of treatment) or disease that is double refractory to a PI and an ImiD. ECOG performance status of 0 or 1 at screening. Cannot have been treated in the prior 3 mo with any anti-CD38 therapy or discontinuation of a prior anti-CD38 therapy at any time due to an AE related to the anti-CD38. 25 study locations in the US, Canada, Germany, Netherlands, and Spain	Teclistamab + D, TalD Teclistamab + PD, TalPD N planned = 200	Primary: DLT incidence and severity, AE and SAE by incidence and severity Secondary: serum concentration of D, teclistamab and tal, biomarker assessment of D, teclistamab, and tal, anti-drug antibodies to D, tec, and tal, ORR, CBR, DOR, TTR	Recruiting
Teclistamab in Japanese population **Open label** **Phase 2** **NCT04696809**	Patients aged ≥20 years with MM according to IMWG diagnostic criteria and measurable disease at screening. Must be relapsed or refractory to established therapies with known clinical benefit in RRMM or be intolerant to established MM therapies and a candidate for teclistamab treatment in the opinion of the treating physician, and ECOG performance status grade of 0 or 1, Prior LOT must include a PI, an IMiD, and an anti-CD38 mAb. Participants who could not tolerate PI, IMiDs, or anti-CD38 antibody are allowed. Japanese study centers	Teclistamab N planned = 9	Primary: Include of AEs, SAEs, and DLT Secondary: serum concentration of teclistamab, systemic cytokine concentrations, patients with anti-teclistamab antibodies, ORR, DOR, TTR	Recruiting

[a] Accurate as of January 11, 2022 based on ClinicalTrials.gov.

Abbreviations: AE = adverse event; BCMA = B-cell maturation antigen; CBR = clinical benefit rate; CR = complete response; CRS = cytokine release syndrome; D = daratumumab; d = dexamethasone; DLT = dose limiting toxicity; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQoL 5 Dimensions, 5 Levels; GHS = global health status; IMWG = International Myeloma Working Group; LOT = line of therapy; mAb = monoclonal antibody; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; OS = overall survival; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PGIS = Patient Global Impression of Severity; PR = partial response; PRO-CTCAE = Patient-reported Outcomes Version of the Common Terminology Criteria for AE; PROMIS PF 8c = Patient-reported Outcomes Measurement Information System Short Form v2.0 - Physical Function 8c; QLQ-C30 = Quality of Life Questionnaire Core-30; R = lenalidomide; rHuPH20 = recombinant human hyaluronidase PH20 enzyme; RP2D = recommended Phase 2 dose; RRMM = relapsed/refractory MM; SAE = serious AE; sCR = stringent CR; tal = talquetamab; TTR = time to response; TTNT = time to next treatment; UK = United Kingdom; US = United States; V = bortezomib; VGPR = very good partial response.

Source: Clinicaltrials.gov [64].

15. Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 62 presents baseline characteristics for MajesTEC-1 and LocoMMotion. See further section 18.1.7, Table 74 for the differences in baseline characteristics for the unadjusted comparison between ITT populations from MajesTEC-1 and the physician's choice whereas Table 75 presents the population differences between MajesTEC-1 and the physician's choice cohort for each of the ranked factors before and after ATT weighting.

Table 62. Baseline characteristics of patients in MajesTEC-1 and LocoMMotion

	MajesTEC-1 (n=165)	LocoMMotion (n=248)
	teclistamab	SoC
Age, median (range) years	64.0 (33.0–84.0)	68.0 (41.0–89.0)
Male, n (%)	96 (58.2)	135 (54.4)
Weight, kg (%)	n= 165	n= 204
Mean (SD)	**75.02 (16.7)**	73.25 (16.341)
Median (range)	73.0 (41.0; 138.9)	73.00 (37.0; 118.9)
Height, cm	n= 165	n= 192
Mean (SD)	**167.42 (11.892)**	167.26 (10.061)
Median (range)	168.0 (123.0; 193.0)	167.00 (147.0; 193.0)
Baseline ECOG score,[a] n (%)	n= 165	n= 248
0	55 (33.3)	65 (26.2)
1	109 (66.1)	179 (72.2)
3	1 (0.6)	1 (0.4)
Time from initial MM diagnosis,[b] median (range) years	6.019 (0.76–22.68)	6.33 (0.3–22.8)
Number of prior lines of therapy, median (range)	5.0 (2.0–14.0)	4.0 (2.0–13.0)
Triple class exposed,[c] n (%)	165 (100)	248 (100)
Refractory status, n (%)	n= 165	n= 248
Any PI	**142 (86.1)**	197 (79.4)
Any IMiD	152 (92.1)	233 (94.0)
Any anti-CD38 mAb	**148 (89.7)**	229 (92.3)
Triple class refractory	**128 (77.6)**	182 (73.4)
Refractory to last line of prior therapy, n (%)	148 (89.7)	230 (92.7)

Sources: [25, 75].

In addition, the baseline characteristics for the proportion (n=63) of patients that switched to Q2W dosing is presented in the table below.

Table 63. Baseline characteristics of patients in MajesTEC-1 for the All Treated Analysis Set (n=165) and for the proportion that switched to Q2W dosing (n=63)

Characteristic	N=165	N=63
Median age, y (range)	64 (33-84)	64 (40-82)
Male, n (%)	96 (58.2)	36 (57.1)
Race		
White	134 (81.2)	55 (87.3)
Black/African American	21 (12.7)	6 (9.5)
Asian	3 (1.8)	1 (1.6)
Not reported/other	7 (4.2)	1 (1.6)
Extramedullary plasmacytomas,a n (%)	28 (17.0)	5 (7.9)
High-risk cytogenetics, n/N (%)	38/148 (25.7)	14/58 (24.1)
ISS stage, n(%)		
I	85/162 (52.5)	43 (68.3)
II	57/162 (35.2)	17 (27.0)
III	20/162 (12.3)	3 (4.8)
Median time since diagnosis, y (range)	6.0 (0.8-22.7)	5.9 (1.1-20.5)
Number of prior LOT, median (range)	5 (2-14)	4 (2-14)

Refractory status, n (%)		
Triple-class[b]	165 (100.0)	47 (74.6)
Penta-drug[c]	50 (30.3)	22 (34.9)

[a]Includes patients who had ≥1 soft-tissue plasmacytoma not associated with bone. [b]>l PI, 21 IMiD, 1 anti-CD38 mAb. [c]02 PIs, 22 IMiDs, 1 anti-CD38 mAb. AE, adverse event; IMiD, immunomodulatory drug ISS International Staging System; LOT, line(s) of therapy; rnAb, monoclonal antibody: PI, proteasome inhibitor, Q2W, every other week; Q4W, every 4 weeks; QW. once weekly.

15.1 Comparability of patients across studies

As previously have been described, an external control arm for MajesTEC-1 was constituted from triple class exposed RRMM patients treated with physician's choice SoC therapies from the LocoMMotion prospective cohort study. In MajesTEC-1, the all treated population consisted of 165 patients and the comparator group was comprised of all patients that received physician's choice derived from LocoMMotion and included 248 subjects who were enrolled in the latter study. These patients are considered to be comparable. In the adjusted comparison, main analyses weighted patients on all of the following factors: refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, age, hemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. Section 18.1.7 presents the population differences between MajesTEC-1 and the LocoMMotion for each of the ranked factors before and after weighting. Following application of IPW-ATT weights to re-weight the LocoMMotion population, the degree of differences between the teclistamab and real-world clinical practice (RWCP)/physician's choice group was reduced, and no imbalances with an SMD > |0.2| remained, where 0.2 is an accepted difference.

15.2 Comparability of the study populations with Danish patients eligible for treatment

The MajesTEC-1 study population is 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 teclistamab. 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 [60].

The baseline characteristics of patients used for the comparative analysis of efficacy and safety (LocoMMotion study) are also considered comparable to the Danish patients eligible for treatment, thus reflecting the eligible patient population. The mean age of 64 at treatment initiation in MajesTEC-1 was assumed to be representative for the Danish patient population relevant for treatment with teclistamab and the median age in MajesTEC-1 is considered representative for the patients that will be treated with Teclistamab, since they are expected to be slightly younger than the overall median age for MM in Denmark, which is tested in a scenario analysis with the health economic analysis.

16. Appendix D Efficacy and safety results per study

Table 64. Definition, validity and clinical relevance of included outcome measures

Endpoint	Definition	Validity	Clinical relevance
Primary Endpoint			
ORR	Defined as the proportion of patients who achieve PR or better according to IMWG criteria, as assessed by the independent review committee.	Adapted from IMWG criteria [40]	Relevant
Secondary Endpoints			
DOR	Calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria, or death due to PD, whichever occurs first. For patients who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.	[116]	Relevant
≥VGPR	Defined as the proportion of patients who achieve a ≥VGPR response according to the IMWG criteria.	IMWG criteria [40]	Relevant
≥CR	Defined as the proportion of patients who achieve a ≥CR response according to the IMWG criteria.	IMWG criteria [40]	Relevant
sCR	Defined as the proportion of patients who achieve a sCR according to the IMWG criteria.	IMWG criteria [40]	Relevant
PR	Defined as the proportion of patients who achieve a PR according to the IMWG criteria.	IMWG criteria [40]	Relevant
TTR	Defined as the time between date of first dose of teclistamab and the first efficacy evaluation that the patient has met all criteria for PR or better.	Adapted from IMWG criteria [40]	Relevant
PFS	Defined as the time from the date of first dose of teclistamab to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For patients who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.	IMWG criteria [40]	Relevant
OS	Defined as the time from the date of first dose of teclistamab to the date of the patient's death. If the patient is alive or the vital status is unknown, then the patient's data will be censored at the date the patient was last known to be alive.[a]	IMWG criteria [40]	Relevant
Exploratory Endpoints			
TTNT	Defined as the time from the date of first dose of teclistamab to the start of the next line treatment.	[117]	Relevant

Patient-reported Outcomes			
Change from baseline in HRQoL as measured by EORTC QLQ-C30	Item and scale scales are reported on a 0 to 100 scale, with higher scores representing better global health status, better functioning, and worse symptoms.b	Validated in Oncology [118]	Relevant
Change from baseline in HRQoL as measured by EQ-5D-5L (utility score and VAS)	A total utility score is reported based on the health status, ranging from 0 to 1, where higher values indicate better health utility. The visual analogue scale ranges from 0 to 100, where higher values indicate better overall health status.	Validated in Oncology [87]	Relevant
Change from baseline in HRQoL as measured by PGI-S (exclusive to MajesTEC-1)	A single verbal rating scale ranges from 1 (a lot better now) to 7 (a lot worse now).	[119]	Relevant
Change from baseline in HRQoL as measured by EORTC QLQ-IL39 (4 items) /Time to improvement/worsening in EORTC QLQ-IL39 (exclusive to LocoMMotion)	The EORTC QLQ-IL39 questionnaire was designed to use alongside the EORTC QLQ-C30 to address issues of more relevance to myeloma patients. It consisted of 4 single items to assess emotional health status (felt restless or agitated, thinking about illness, worried about dying, worried about health in the future). This questionnaire includes four single items from the EORTC QLQMY20. Improvement in EORTC QLQ-IL39 was defined as a decrease or increase (depending on the item) from baseline of ≥10 points	EORTC QLQMY20 is a validated tool [120]	Relevant
Safety Endpoints			
Number of participants with AEs	An AE is defined is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.	ICH [121]	Relevant
Number of participants with SAEs	A SAE is defined as any untoward medical occurrence that at any dose: • Results in death • Is life-threatening (the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe) • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability/incapacity • Is a congenital anomaly/birth defect • Is a suspected transmission of any infectious agent via a medicinal product • Is medically important • If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event	ICH [121]	Relevant

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	must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Note: In LocoMMotion another endpoint was included – Clinical Benefit Rate (CBR) defined as the proportion of patients who achieved minimal response or better according to the IMWG criteria, as assessed by a response review committee.

[a] In LocoMMotion, participants who died after consent withdrawal were considered as having an OS event. [b] In LocoMMotion the EORTC QLQ-C30 instrument was used to measure overall meaningful change from baseline, defined as meaningful improvement achieved at least once during the SOC treatment.

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16.1 Results per study

The efficacy results for MajesTEC-1 are presented in Table 65 and for LocoMMotion in Table 66. Safety results are presented in section 7.3.7 and 7.4.2 and utilities in section 8.4. PRO are presented in Appendix K Patient reported outcomes.

Table 65. Summary of main efficacy results for MajesTEC-1

Outcome	January 4, 2023 cut-off All Treated Analysis Set (n=165)
PFS	
Number of events, n (%)	102 (61.8%)
Number of events censored, n (%)	63 (38.2%)
Median Kaplan–Meier estimate, mo	
25% percentile (95% CI)	2.1 (1.2, 4.3)
Median (95% CI)	11.3 (8.8, 16.4)
75% percentile (95% CI)	NE (25.9, NE)
6-month progression-free survival rate % (95% CI)	64.4 (56.4, 71.3)
9-month progression-free survival rate % (95% CI)	56.5 (48.3, 63.9)
12-month progression-free survival rate % (95% CI)	48.6 (40.5, 56.2)
18-month progression-free survival rate % (95% CI)	39.9 (32.1, 47.5)
24-month progression-free survival rate % (95% CI)	33.7 (25.9, 41.6)
OS	
Number of events (%)	84 (50.9%)
Number of censored (%)	81 (49.1%)
Kaplan-Meier estimate (months)	
25% percentile (95% CI)	8.8 (4.2, 10.8)
Median (95% CI)	21.9 (15.1, NE)
75% percentile (95% CI)	NE (28.3, NE)
6-month overall survival rate % (95% CI)	77.8 (70.6, 83.4)
9-month overall survival rate % (95% CI)	74.7 (67.2, 80.7)
12-month overall survival rate % (95% CI)	64.0 (56.0, 70.9)
18-month overall survival rate % (95% CI)	54.5 (46.4, 61.8)
24-month overall survival rate % (95% CI)	48.7 (40.5, 56.3)
Response Rates[a], n (%; 95% CI)	n = 165
ORR (sCR + CR + VGPR + PR)	104 (63.0%; 55.2, 70.4)
≥VGPR (sCR + CR + VGFR)	98 (59.4%; 51.5, 67.0)
≥CR (sCR + CR)	75 (45.5%;37.7, 53.4)
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	23 (13.9%; 9.0, 20.2)
Not evaluable	8 (4.8%; 2.1, 9.3)
Time to response	
Time to first response, mo	
Mean (SD)	1.45 (0.885)
Median (range)	1.18 (0.2; 5.5)
n	104
Time to best response, mo	
Mean (SD)	6.10 (4.718)
Median (range)	3.96 (1.1; 18.7)
n	104

Time to ≥VGPR, mo	
Mean (SD)	2.91 (2.480)
Median (range)	2.23 (0.2; 18.5)
n	98
Time to ≥CR, mo	
Mean (SD)	6.47 (4.808)
Median (range)	4.63(1.6; 18.5)
n	75
Duration of response	
DOR in Responders[a]	n = 104
Number of events[b], n (%)	50 (48.1%)
Number of censored, n (%)	54 (51.9%)
Median Kaplan–Meier DOR estimate	
25% percentile (95% CI)	9.5 (7.6, 13.5)
Median (95% CI)	21.6 (16.2, NE)
75% percentile (95% CI)	NE (26.7, NE)
Range	(1, 32+)
6-month event-free rate % (95% CI)	90.3 (82.7, 94.6)
9-month event-free rate % (95% CI)	80.5 (71.4, 86.9)
12-month event-free rate % (95% CI)	69.7 (59.8, 77.6)
18-month event-free rate % (95% CI)	58.5 (48.3, 67.4)
24-month event-free rate % (95% CI)	49.9 (39.0, 59.9)

a Response assessed by IRC based on IMWG consensus criteria (2016).
Abbreviations: CI = confidence interval; CR = complete response rate; IMWG = International Myeloma Working Group; MR = minimal response; NE = not estimable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = Progression free survival; PR = partial response; sCR = stringent CR; SD = stable disease; VGPR = very good partial response.
Sources: [69]

Table 66. Summary of main efficacy results for LocoMMotion

Outcomes	October 27 2022 cut-off n=248
Progression-free survival	
Number of events (%)	171 (69.0%)
Number of censored (%)	77 (31.0%)
Kaplan-Meier estimate (months)	
25% quantile	2.04 (1.68, 2.56)
Median	4.63 (3.94, 5.62)
75% quantile	9.92 (8.18, 13.86)
6-month progression-free survival rate %	40.9 (34.1, 47.7)
12-month progression-free survival rate %	21.0 (15.3, 27.3)
18-month progression-free survival rate %	14.0 (9.1, 20.0)
24-month progression-free survival rate %	10.5 (6.1, 16.3)
Overall survival	
Number of events (%)	158 (63.7%)
Number of censored (%)	90 (36.3%)
Kaplan-Meier estimate (months)	
25% quantile	5.72 (4.83, 6.44)
Median	13.83 (10.84, 16.99)
75% quantile	30.95 (24.57, NE)
6-month overall survival rate %	73.1 (67.0, 78.2)
12-month overall survival rate %	53.4 (46.7, 59.6)
18-month overall survival rate %	42.5 (35.9, 49.0)
24-month overall survival rate %	33.7 (27.3, 40.2)
Response Rates, n (%; 95% CI)	
ORR (sCR + CR + VGPR + PR)	79 (31.9%; 26.1, 38.0)

sCR	0 (NE, NE)
CR	1 (0.4%; 0.0, 2.2)
VGPR	32 (12.9%; (9.0, 17.7)
PR	46 (18.5; (13.9, 24.0)
MR	14 (5.6%;(3.1, 9.3)
SD	78 (31.5%;25.7, 37.6)
PD	43 (17.3%;12.8, 22.6)
Not evaluable	34 (13.7%; 9.7, 18.6)
Time to response (defined as PR or better)	
Number of events (%)	79 (31.9%)
Number of censored (%)	169 (68.1%)
Kaplan-Meier estimate (months)	
25% quantile	2.33 (1.87, 2.79)
Median	5.65 (3.91, 9.53)
75% quantile	25.79 (9.53, NE)

a Note: Response was assessed by response review committee (RRC), based on International Myeloma Working Group (IMWG) consensus criteria (2016). Percentages are calculated with the number of participants in the analysis set as denominator. Exact 95% confidence intervals are provided.

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response SoC = Standard of care; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; sCR = stringent CR; VGPR = very good partial response. Source: [71]

17. Appendix E Safety data for intervention and comparator(s)

Section presented safety data from MajesTEC-01 and LocoMMotion, Table 67 below present an overview of total TEAEs and grade 3 and 4 TEAEs from LocoMMotion .

Table 67. Treatment-emergent Adverse Events in ≥5% of participants by System Organ Class and Preferred Term (Total and Toxicity Grade of 3 or 4); LocoMMotion (n=248)

Treatment-emergent Adverse Events in ≥5%	Total	Grade 3 or 4
Total number of participants with TEAE	215 (86.7%)	144 (58.1%)
MedDRA system organ class/preferred term		
Blood and lymphatic system disorders	124 (50.0%)	101 (40.7%)
Thrombocytopenia	65 (26.2%)	48 (19.4%)
Anemia	64 (25.8%)	27 (10.9%)
Neutropenia	50 (20.2%)	43 (17.3%)
Leukopenia	22 (8.9%)	15 (6.0%)
Lymphopenia	21 (8.5%)	19 (7.7%)
General disorders and administration site conditions	101 (40.7%)	16 (6.5%)
Pyrexia	33 (13.3%)	6 (2.4%)
Fatigue	31 (12.5%)	2 (0.8%)
Asthenia	24 (9.7%)	3 (1.2%)
Oedema peripheral	24 (9.7%)	1 (0.4%)
Gastrointestinal disorders	83 (33.5%)	9 (3.6%)
Diarrhea	40 (16.1%)	2 (0.8%)
Nausea	25 (10.1%)	3 (1.2%)
Constipation	14 (5.6%)	0
Vomiting	14 (5.6%)	2 (0.8%)
Infections and infestations	82 (33.1%)	20 (8.1 %)
Musculoskeletal and connective tissue disorders	67 (27.0%)	15 (6.0%)
Back pain	26 (10.5%)	4 (1.6%)
Arthralgia	20 (8.1%)	3 (1.2%)
Bone pain	13 (5.2%)	2 (0.8%)
Nervous system disorders	60 (24.2%)	8 (3.2%)
Peripheral sensory neuropathy	15 (6.0%)	2 (0.8%)
Respiratory, thoracic and mediastinal disorders	55 (22.2%)	14 (5.6%)
Dyspnea	29 (11.7%)	5 (2.0%)
Metabolism and nutrition disorders	37 (14.9%)	9 (3.6%)
Injury, poisoning and procedural complications	30 (12.1%)	10 (4.0%)
Psychiatric disorders	26 (10.5%)	3 (1.2%)
Renal and urinary disorders	25 (10.1%)	14 (5.6%)
Investigations	24 (9.7%)	7 (2.8%)
Skin and subcutaneous tissue disorders	23 (9.3%)	1 (0.4%)
Vascular disorders	22 (8.9%)	7 (2.8%)
Cardiac disorders	18 (7.3%)	8 (3.2%)
Eye disorders	18 (7.3%)	4 (1.6%)

Source: [75].

18. Appendix F Comparative analysis of efficacy and safety

18.1 Adjusted comparison

The objective of adjusted comparison was to evaluate the comparative efficacy of teclistamab (as assessed in MajesTEC-1) versus physician's choice of treatment (as assessed in LocoMMotion) for the treatment of patients with triple class exposed RRMM.

18.1.1 Data Sources and patient populations

This study used individual patient-level data (IPD) from MajesTEC-1 and the prospective real-life SOC study, LocoMMotion. Participants included in the MajesTEC-1 and physician's choice cohorts were required to satisfy the key criteria outlined in Table 68.

Table 68. Key Eligibility Criteria for MajesTEC-1 and Physician's Choice Cohorts

Key Eligibility Criteria	MajesTEC-1 Cohort	Physician's Choice Cohort
RRMM diagnosis as defined by IMWG	Required	Required
Number of prior lines of treatment	Received at least three prior MM treatment lines [1; 2]	Received at least three prior MM treatment lines [1; 2], or double refractory to a PI and an IMiD
Triple class exposed	Received as part of previous therapy a PI, an IMiD, and an anti-CD38 MoAB (prior exposure can be from different monotherapy or combination lines of treatment)	Received as part of previous therapy a PI, an IMiD, and an anti-CD38 MoAB (prior exposure could be from different monotherapy or combination regimens)
ECOG score	0,1	0,1
Creatinine levels	≤ 1.5 mg/dL or creatinine clearance>=40 mL/min/1.73m	
Hemoglobin	> 8 g/dL	
Evidence of PD	Documented evidence of PD (based on investigator assessment of response by IMWG criteria) on or within 12 months of most recent lines of treatment. Note: participants with documented evidence of PD within the previous 6 months and who were refractory or non-responsive to their most recent lines of treatment afterwards were also eligible.	Documented evidence of PD (based on response review committee assessment of response by IMWG criteria) on or within 12 months of most recent lines of treatment.

[1] Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered one line of treatment
[2] Undergone at least one complete cycle of treatment for each prior line of treatment, unless PD was the best response to the lines of treatment
Abbreviations: ECOG = Eastern Cooperative Oncology Group; ImiD = immunomodulatory drug; IMWG = International Myeloma Working Group; MM = multiple myeloma; MoAB= monoclonal antibody; PD = progressive disease; PI = proteasome inhibitor; RRMM = relapsed or refractory multiple myeloma.

The ITT populations in MajesTEC-1 and the physician's choice cohort were considered analogous and were compared in the current analyses. The ITT population in MajesTEC-1 included all participants who were treated with teclistamab with the index date defined as the date of first dose. The ITT population in the physician's choice cohort consisted of all participants who satisfied the eligibility criteria outlined above, with the index date defined as Day 1 Cycle 1 of the real-life SOC treatment.

18.1.2 Outcome

The present adjusted comparison considered seven efficacy outcomes: ORR, ≥CR rate, VGPR or better (≥VGPR) rate, PFS, DoR, TTNT, and OS.

18.1.2.1 Overall Response Rate

In both data sources, ORR was defined as the proportion of participants who achieved a PR or better according to the IMWG criteria [122]. ORR was adjudicated by the IRC for MajesTEC-1 and by an RRC for the physician's choice cohort. In the MajesTEC-1 cohort, response after the start of subsequent therapy or retreatment with teclistamab was not considered.

18.1.2.2 Complete Response or Better

In both data sources, ≥CR rate was defined as the percentage of participants achieving CR or sCR according to IMWG criteria [122]. CR and sCR were adjudicated by the IRC for MajesTEC-1 and by an RRC for the physician's choice cohort.

18.1.2.3 Very Good Partial Response or Better

In both data sources, ≥VGPR rate was defined as the percentage of participants achieving VGPR or better response according to IMWG criteria. VGPR or better rate was adjudicated by the IRC for MajesTEC-1 and by an RRC for the physician's choice cohort.

18.1.2.4 Duration of Response

In both sources, DoR was defined according to IMWG criteria 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. 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. DoR was adjudicated by the IRC for MajesTEC-1 and by an RRC for the physician's choice cohort.

18.1.2.5 Time to Next Treatment

In both sources, TTNT was defined as the time from the index date to the initiation of the next therapy line or death, whichever occurred first. 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.

18.1.2.6 Progression-free Survival

In both data sources, PFS was defined as the duration 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-off, were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy. PFS was evaluated according to IMWG criteria in both data sources and was adjudicated by the IRC for MajesTEC-1 and by an RRC for the physician's choice cohort.

18.1.2.7 Overall Survival

In both data sources, OS was defined as the time from the index date to the date of the participant's death. Patients still alive or the vital status was unknown were censored at the date last known to be alive.

18.1.3 Methodology

18.1.3.1 Identification and Rank Ordering of Prognostic Factors

Imbalances in baseline participant characteristics between the MajesTEC-1 and physician's choice cohorts can lead to biased comparative efficacy estimates if left unadjusted, due to confounding driven by factors that differ substantially across participant populations and are prognostic of the outcomes. The steps undertaken for identifying and rank-ordering prognostic factors are outlined below.

1. Prior to conducting the analyses, a pool of potential prognostic variables was identified by consulting studies from a literature review conducted to identify clinical outcomes in triple class exposed RRMM patients, as well as input from clinical experts.
2. Analyses including all available variables with sufficient data were considered as the "Main Analysis".
3. Variables with a high degree of missingness were adjusted for as a sensitivity analysis. These factors were ranked according to availability and level of missingness within the included studies.

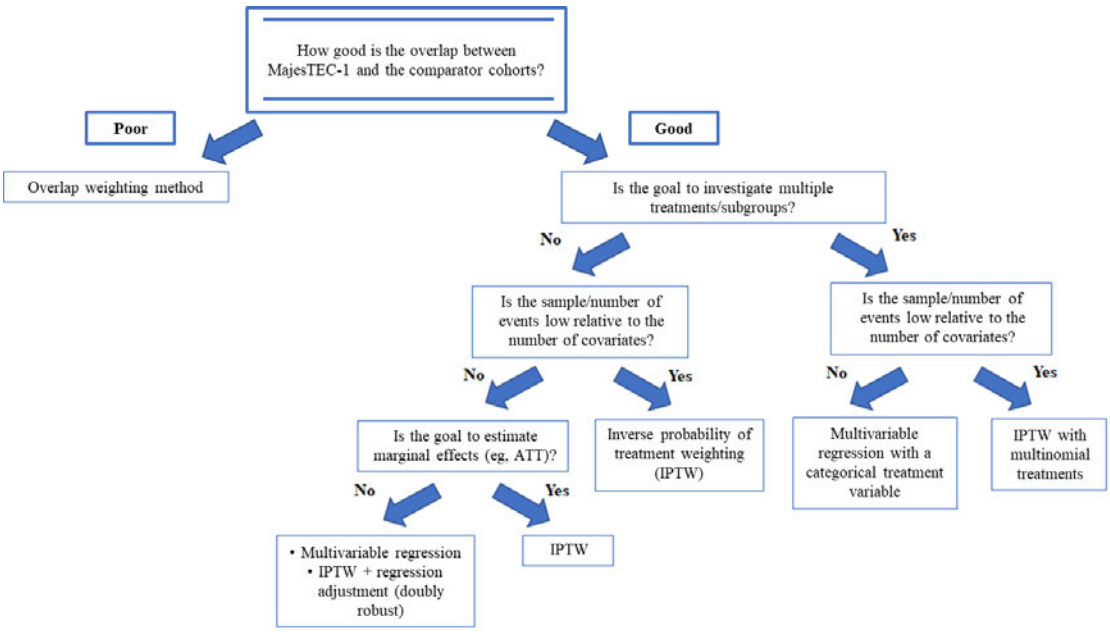
18.1.3.2 Handling Missing Data in Selected Prognostic Factors

For variables with less than 25% of values missing, low risk imputation was used to impute missingness for teclistamab, and mode value was used to impute missingness for the physician's choice cohort. Variables requiring imputation for the MajesTEC-1 population were (proportion of missing data in parentheses): International Staging System (ISS) stage (1.8%), years since MM diagnosis (0.6%), time to progression on last regimen (1.2%), and average duration of prior lines (0.6%). For the physician's choice cohort from LocoMMotion several variables required imputation (proportion of missing data in parentheses): ECOG status (1.2%), ISS stage (12.5%), hemoglobin levels (10.1%), creatinine clearance (5.2%), lactate dehydrogenase (LDH) levels (23.8%), type of MM (16.5%), and race (23.4%).

18.1.3.3 Choice of statistical method

To ensure a balance in baseline characteristics between participants in the MajesTEC-1 and physician's choice cohorts at the index date, selected prognostic factors were adjusted for using either propensity score or regression methods. The algorithm in
Figure 50 guided the decision on which statistical method to use to compare teclistamab versus physician's choice of treatment. Per this algorithm, poor overlap of prognostic factors between patient populations is to be corrected through a matching procedure [123].

Figure 50. Algorithm for selection of statistical techniques to compare treatments adapted from NICE TSD



Source: NICE TSD 17 [123].
Abbreviations: ATT, average treatment effect in the treated; IPTW, inverse probability of treatment weighting; NICE, National Institute for Health and Care Excellence; TSD, technical support document.

Since the LocoMMotion trial was prospectively designed to recruit a patient population similar to that of MajesTEC-1, there is enough overlap between patient characteristics despite several large standardized mean differences (SMDs) to justify weighting techniques that do not depend on matching.

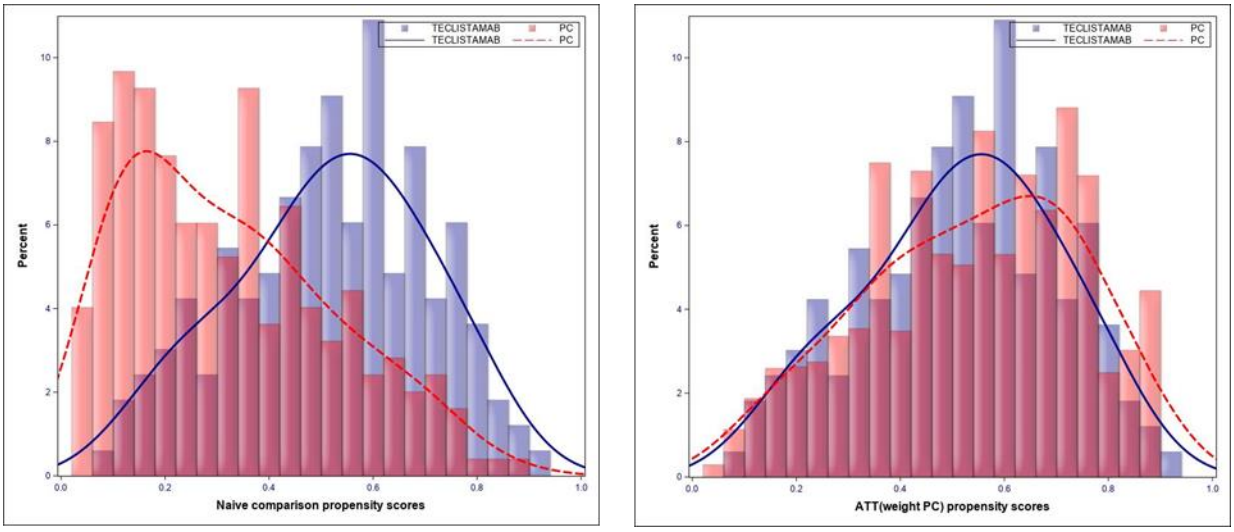
- Inverse probability of treatment weighting (IPTW) with average treatment effect in the treated (ATT) weighting was chosen for the main analyses. This propensity-score based method allowed the physician's choice cohort to be reweighted to align with the MajesTEC-1 population. IPTW was possible given the overlap in the covariate distribution between the two cohorts, and is an efficient method when the sample size is small relative to the number of potential baseline confounding factors.[124] Due to small sample size, treatment weightings were scaled such that they summed to the original number of patients in the physician's choice cohort, allowing analyses to rely on an adjusted population equivalent in sample size. Average treatment effect for overlap (ATO) was conducted as a sensitivity analysis.
- Multivariable regression was also conducted as a sensitivity analysis. Similar to IPTW, this method requires as well sufficient overlap in the covariate distribution between the two cohorts; however, unlike IPTW with ATT weights, the regression models estimated the conditional average treatment effect. 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 covariates.
- Additional details on each statistical method are provided below.
- All statistical analyses and graphical interpretation of the results were conducted using R version 3.6.1 and 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and SAS version 9.4 (SAS Institute, Cary, North Carolina).

18.1.3.4 Inverse Probability of Treatment Weighting - Model Specifications

18.1.3.4.1 Weighting

The propensity score is a balancing score defined by Rosenbaum and Rubin as the probability of treatment assignment conditional on observed baseline covariate: $e_i = Pr(Z_i = 1|X_i)$ [74]. 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 logistic regression using each cohort (MajesTEC-1 versus the physician's choice cohort) as the dependent variable and selected baseline covariates as explanatory variables. 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 MajesTEC-1 ITT population and the LocoMMotion physician's choice cohort as evaluated by comparing unweighted and weighted propensity score distributions (Figure 51), as well as unweighted and weighted SMD plots for the physician's choice cohort (Figure 53).

Figure 51. Distributional Balance for the Unadjusted and Adjusted Main Analysis



Abbreviations: ATT, average treatment effect in the treated; PC, physician's choice

18.1.3.4.2 Target Populations

The current analysis estimated the ATT population. The weights for participants in the MajesTEC-1 cohort were $\widehat{ATTw}_{1k} = 1$ $(k = 1, 2, \cdots, n_1)$, and the weight for participants in the physician's choice cohort 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 MajesTEC-1 and the physician's choice cohort, respectively [73]. For DoR, the sample sizes only included patients that achieved at least ORR. A sensitivity analysis estimating the ATO was conducted with $\widehat{ATOw}_{1k} = 1 - p_{0k}$ $(k = 1, 2, \cdots, n_1)$ and $\widehat{ATOw}_{0k} = p_{0k}$ $(k = 1,2, \cdots, n_0)$, where p_1 was the overlap population [73].

18.1.3.4.3 Estimating Adjusted Treatment Effect

The comparative efficacy of teclistamab versus physician's choice of treatment was determined in terms of ORR, ≥CR rate, ≥VGPR rate, PFS, DoR, TTNT, and OS. Estimates of comparative efficacy were derived for both the unadjusted comparison (i.e., teclistamab versus physician's choice of treatment prior to IPTW), and the adjusted comparison (i.e., with IPTW). For the binary outcomes (e.g., ORR, ≥CR rate, and ≥VGPR rate), a weighted logistic regression was used to derive an odds ratio (OR) with its respective 95% confidence interval (CI), transformed to response-rate ratio (RR) [125]. For the time-to-event outcomes (e.g., PFS, DoR, TTNT, and OS), a weighted Cox proportional hazards model was used to derive a hazard ratio (HR) and its respective 95% CI.

18.1.3.5 Multivariate regression Models as Sensitivity Analyses

18.1.3.5.1 Model Specifications

Multivariable regressions were conducted including a binary treatment indicator (teclistamab or physician's choice of treatment) and covariates for adjustment in the model.

18.1.3.5.2 Estimating Adjusted Treatment Effect

The comparative efficacy of teclistamab versus physician's choice of treatment was estimated in terms of ORR, ≥CR rate, ≥VGPR rate, PFS, DoR, TTNT, and OS. For the binary outcomes (e.g., ORR, ≥CR rate, and ≥VGPR rate), an unweighted logistic regression including the selected baseline characteristics as covariates was used to estimate the OR with its respective 95% CI. For the time-to-event outcomes (e.g., PFS, DoR, TTNT, and OS), an unweighted Cox proportional hazards model including the selected baseline characteristics as covariates was used to derive the HR and its respective 95% CI. The variance was estimated using a robust sandwich variance estimator [73, 124]. For all time-to-event analyses, observed and weighted survival curves were reported, including the number of patients at risk across time, as well as increased uncertainty in the survival curves across time.

18.1.3.6 Scenario Analysis

A scenario analysis was conducted to investigate the impact on the treatment effect estimates and balance of participant populations when adjusting for additional covariates in the analyses. The main analysis contained all covariates which were available for adjustment and for which did not have a high level of missing values. Separate adjusted comparisons were conducted, adjusting for all available covariates (referred to as the "Sensitivity Analysis Including All Variables").

18.1.3.7 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 [126] (with a p-value less than 0.05 considered to indicate a violation of the assumption). If there is clear evidence that the proportional hazards assumption did not hold, this indicates that the HR changes over time and the overall HR across the entire observed follow-up period may not be a good summary measure for the treatment effect. In such cases, a time dependent Cox proportional hazards regression model will be considered, to estimate HR by time periods [127].

18.1.3.8 Sensitivity Analyses using ATO

In addition to the regression sensitivity analysis, IPTW with ATO weighting was conducted and is summarized in Table 69. All analyses were conducted for all outcomes of interest (ORR, ≥CR rate, ≥VGPR rate, PFS, DoR, TTNT, and OS).

Table 69. Overview of Sensitivity Analyses

	Analytic Specification				
	Populations	**Outcomes**	**Handling of missing data**	**Statistical method**	**Included lines of treatment for participants in the physician's choice cohort**
Main Analyses	ITT	ORR, ≥CR rate, ≥VGPR rate, PFS, DoR, TTNT, and OS	Imputation for variables with <25%, excluding variables with ≥25% categories that include missingness	IPTW with ATT weights	One line of treatment per patient
Sensitivity Analyses					
Multivariable Regression	Unchanged	Unchanged	Unchanged	Multivariable Regression	Unchanged
IPTW with ATO weighting	Unchanged	Unchanged	Unchanged	IPTW with ATO weighting	Unchanged
Including All Variables	Unchanged	Unchanged	Including variables with ≥25% categories that include missingness	Unchanged	Unchanged

Note: "unchanged" indicates that the analytic specification was unchanged from the main analyses.
Abbreviations: ATO, average treatment effect in the overlap; ATT, average treatment effect in the treated; ≥CR, complete response or better; DoR, duration of response; IPTW, inverse probability of treatment weighting; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment; ≥VGPR, very good partial response or better

18.1.4 Selection of Participants

Participants were selected from MajesTEC-1 (MajesTEC-1 cohort) and the prospective real life SOC study, LocoMMotion (physician's choice cohort) according to the inclusion criteria outlined in Figure 52. For the MajesTEC-1 cohort, the ITT population consisted of all 165 patients who were treated with teclistamab 1.5 mg/kg SC. The physician's choice cohort from LocoMMotion included a total of 248 participants.

18.1.5 Treatments Received Across all Eligible lines of treatment in the Physician's Choice Cohort

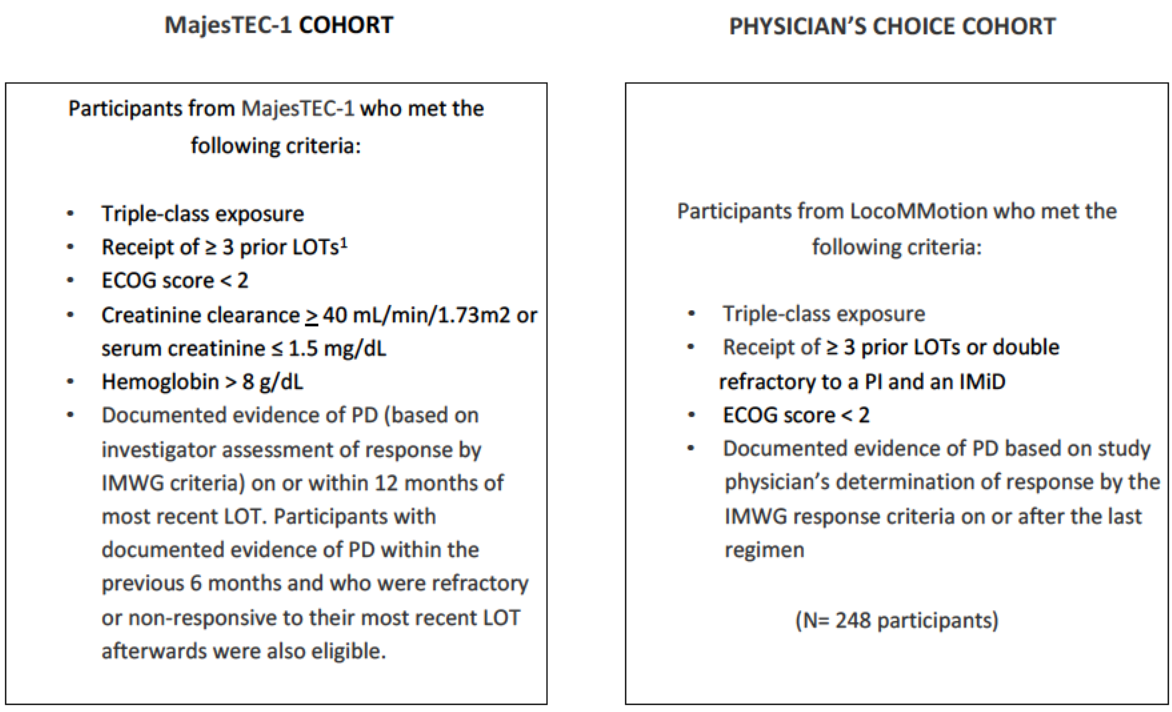
The treatments received by the ITT population of the physician's choice cohort are summarized in Table 70. Carfilzomib plus dexamethasone, cyclophosphamide plus dexamethasone plus pomalidomide and dexamethasone plus pomalidomide, were the three regimens prescribed to the largest proportion of patients (14.1%, 14.1% and 10.9%, respectively). Most patients were prescribed combination regimens, however a handful received monotherapies such as melphalan (1.6%) and belantamab mafodotin (1.6%). Regimens that were prescribed to less than four patients were left out of Table 70 for brevity, with most of them being combination therapies only prescribed to one or two patients.

Table 70. Treatment Regimens in the LocoMMotion Physician's Choice Cohort (≥4 Patients).

Treatment Regimen	Frequency (%)
Carfilzomib-Dexamethasone	35 (14.1%)
Cyclophosphamide-Dexamethasone-Pomalidomide	35 (14.1%)
Dexamethasone-Pomalidomide	29 (11.7%)
Dexamethasone-Ixazomib-Lenalidomide	14 (5.6%)
Bortezomib-Dexamethasone-Panobinostat	11 (4.4%)
Bendamustine-Bortezomib-Dexamethasone	7 (2.8%)
Carfilzomib-Cyclophosphamide-Dexamethasone	7 (2.8%)
Dexamethasone-Elotuzumab-Pomalidomide	6 (2.4%)
Dexamethasone-Lenalidomide	6 (2.4%)
Bortezomib-Dexamethasone-Doxorubicin	5 (2.0%)
Carfilzomib-Dexamethasone-Lenalidomide	5 (2.0%)
Carfilzomib-Dexamethasone-Pomalidomide	5 (2.0%)
Belantamab Mafodotin	4 (1.6%)
Bendamustine-Prednisone	4 (1.6%)
Cyclophosphamide-Dexamethasone	4 (1.6%)
Melphalan	4 (1.6%)

Note: Percentages are calculated with the number of participants in the all-treated analysis set as denominator (N=248). Participants can be counted in more than one regimen or combination if they have received more than one combination in their treatment before progression or death.
Source: [71]

Figure 52. Participant Selection Procedure based on key eligibility criteria



[1] MajesTEC-1 included 5 patients (out of 165) with 2 prior lines

18.1.6 Identification and Rank Ordering of Prognostic Factors for Balancing

A list of potentially important prognostic factors was created as described above. The list of factors and their availability in MajesTEC-1 and the physician's choice cohort is shown in
Table 71. Of the seventeen factors, all were available for both MajesTEC-1 as RWPC cohort. However, two of these factors were not included in the main analysis. Cytogenetic risk missing in 38% of the RWPC, reflecting this is not systematically assessed in real life clinical practice. In addition, race was also not included in the primary analysis, as inclusion induced unstable estimates and increased imbalance for other factors. This was caused by the high weights assigned to the small number of non-white patients enrolled in LocoMMotion, in order to balance with the higher proportion of non-white patients in MajesTEC-1See Table 72 for detailed variable descriptions. However, both variables were still included in a sensitivity analysis including all 17 variables. For variables with less than 25% of values missing, missing values were imputed (see Table 73). The available factors were then ranked from most to least important using an evidence-informed process, as described in Methodology. This process yielded one final ranking that could be applied across all outcomes of interest (
Table 71), thereby providing consistency across analyses.

Table 71. Final Ranking of Prognostic Factors and Availability in MajesTEC-1 and Physician's Choice Cohort

Prognostic Factor	Rank	Available in MajesTEC-1?	Available in Physician's Choice Cohort?	Categories
Refractory status[1]	Required*	Yes	Yes	Penta refractory: at least 2 IMiDs, 2 PIs, and an anti-CD38 MoAB Quad refractory: 2 IMiDs and 2 PIs Triple refractory: at least 1 IMiD, 1 PI, and 1 anti-CD38 MoAB ≤ Double refractory: up to and including 1 IMiD and 1 PI
ISS stage	Required*	Yes	Yes	I II III
Time to progression on last regimen	Required*	Yes	Yes	< 3 months ≥ 3 months
Extramedullary plasmacytoma[2]	Required*	Yes	Yes	Yes No
Number of prior lines of treatment	Required*	Yes	Yes	≤ 4 > 4
Years since MM diagnosis	Required*	Yes	Yes	< 6 ≥ 6
Average Duration of Prior Lines (months)	Required*	Yes	Yes	< 10 10-14 ≥ 15
Age	Required*	Yes	Yes	< 65 ≥ 65
Hemoglobin (g/dL)	Required*	Yes	Yes	< 12 ≥ 12
LDH levels (units/L)	Required*	Yes	Yes	< 280 ≥ 280
Creatinine Clearance	Required*	Yes	Yes	<60 60 to <90 ≥ 90
ECOG status	Required*	Yes	Yes	0 1
Sex	Required*	Yes	Yes	Male Female
Type of MM	Required*	Yes	Yes	IgG Non-IgG
Prior stem cell transplant	Required*	Yes	Yes	Yes

				No
Race	16	Yes	Yes (Missing values)	White Other/Not reported
Cytogenetic Risk Profile	17	Yes	Yes (Missing values)	Standard risk: any other abnormality High risk: at least one of del17p, t(4;14), or t(14;16) Missing

* Variables labelled "required" were considered equally important by clinical experts and were included in the Main Analysis.
1 Refractoriness was defined as from the case report form as progressive disease/relapse (physician's choice cohort) and by International Myeloma Working Group consensus criteria (MajesTEC-1) [68].
2 Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas [128].
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; MoAB, monoclonal antibody; NA, not applicable; PI, proteasome inhibitor

Table 72. Variable Description in MajesTEC-1

Variable	Description	Timepoint of Assessment
Refractory status	Penta refractory: at least 2 IMiDs, 2 PIs, and an anti-CD38 MoAB Quad refractory: 2 IMiDs and 2 PIs Triple refractory: 2 IMiDs and 1 PI; or 2 PIs and 1 IMiD ≤ Double refractory: two or less treatments	Index date[a]
ISS stage[b]	I: β_2M < 3.5 mg/L and ALB ≥ 3.5 g/dL II: β_2M < 3.5 mg/L and ALB < 3.5 g/d; or β_2M 3.5 to <5.5, irrespective of ALB III: β_2M ≥ 5.5 mg/L	Index date[a]
Time to progression on last regimen	≤ 3 months > 3 months	Index date[a]
Extramedullary plasmacytoma	Yes: presence of extramedullary plasmacytomas (refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas[128]) No: no presence of extramedullary plasmacytomas	Index date[a]
Number of prior lines of treatment	≤ 4 prior lines of MM therapy > 4 prior lines of MM therapy	Index date[a]
Years since MM diagnosis	< 6 years since MM diagnosis ≥ 6 years since MM diagnosis	Index date[a]
Average duration of prior lines of treatment	< 10 months 10-14 months ≥ 15 months	Index date[a]
Age	< 65 years ≥ 65 years	Index date[a]
Hemoglobin	< 12 g/dL ≥ 12 g/dL	Index date[a]
LDH levels	<280 units/L ≥280 units/L	Index date[a]
Creatinine Clearance	<60 mL/min 60 to <90 mL/min ≥90 mL/min	Index date[a]
ECOG status	ECOG status of 0 ECOG status of 1	Index date[a]
Sex	Male Female	Index date[a]
Type of MM	IgG Non-IgG	Index date[a]
Prior stem cell transplant	Yes: participant had a prior stem cell transplant (autologous or allogeneic) No: participant did not have a prior stem cell transplant (autologous or allogeneic)	Index date[a]
Race	White Other or not reported	Index date[a]
Cytogenetic profile	High risk: at least one of del17p, t(14;16), t(4;14)	Index date[a]

Standard risk: any other abnormality
Unknown: missing or not documented

[a] Time of start of study drug
[b] As defined by Greipp et al. [129].
Abbreviations: ALB, serum albumin; β2M, serum β-2 microglobulin; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; MoAB, monoclonal antibody; PI, proteasome inhibitor

Table 73. Imputation of Missing Values in Selected Prognostic Factors

	MajesTEC-1 (ITT)			Physician's Choice Cohort (ITT)		
Variable	Missing n (%)	Original n (%)	Imputed n (%)	Missing n (%)	Original n (%)	Imputed n (%)
Age	-			-		
Sex	-			-		
Years since MM diagnosis	1 (0.6%)	164 (99.4%)	165 (100%)	-		
Number of prior lines of therapy	-			-		
ECOG status	-			3 (1.2)	245 (98.8)	248 (100)
ISS stage	3 (1.8%)	162 (98.2%)	165 (100%)	31 (12.5)	217 (87.5)	248 (100)
Type of MM	-			41 (16.5)	207 (83.5)	248 (100)
Extramedullary plasmacytoma	-			-		
Prior stem cell transplant	-			-		
Refractory status	-			-		
Time to progression on last regimen (months)	2 (1.2%)	163 (98.8%)	165 (100%)	-		
Cytogenetic profile	17 (10.3%)	148 (89.7%)	-	94 (37.9%)	154 (62.1%)	-
Hemoglobin (g/dL)	-			25 (10.1)	223 (89.9)	248 (100)
LDH levels at the index date (units/L)	-			59 (23.8)	189 (76.2)	248 (100)
Creatinine Clearance	-			13 (5.2)	235 (94.8)	248 (100)
Average Duration of Prior Lines (months)	1 (0.6%)	164 (99.4%)	165 (100%)	-		
Race	-	-	-	58 (23.4%)	190 (76.6%)	-

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MM, multiple myeloma

18.1.7 Balance of Populations in the Main Analysis and Sensitivity Analysis Including All Variables

The main analysis weighted participants on the following factors: refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of treatment, years since MM diagnosis, average duration of prior lines, age, hemoglobin levels, LDH levels, creatinine clearance, ECOG status, sex, type of MM, and prior stem cell transplant. The sensitivity analysis including all variables weighted participants on race and cytogenetic profile, in addition to variables from the main analysis.

Table 75 shows the population differences between MajesTEC-1 and the physician's choice cohort for each of the ranked factors before and after ATT weighting. Before reweighting, moderate (0.1< SMD ≤0.2) to substantial (SMD >0.2) differences were observed for many of the main analysis variables, with the MajesTEC-1 population having a higher proportion of participants with ISS stage I disease, with immunoglobulin G subtype, who were under 65 years of age, who were quad- and penta-refractory, who had a prior stem cell transplant, and who had creatinine clearance

between 60 and 90 mL/min. In contrast to MajesTEC-1, the physician's choice cohort had a greater proportion of participants with ISS stage III disease, who were triple refractory, and who had creatinine clearance <60 mL/min.

Main analysis reweighting of the physician's choice cohort resulted in more balance between the participant populations with respect to the weighted and unweighted factors. Considering all factors, the mean SMD reduced from 0.206 prior to weighting to 0.048 after weighting. The proportion of categories with SMDs >0.1 reduced from 67% to 7%, and the proportion of categories with SMDs >0.2 also reduced from 40% to 0% (see table Table 74).

Table 74. Differences in Unadjusted Baseline Characteristics between ITT Populations from MajesTEC-1 and the Physician's Choice Cohort

Variable	Categories	MajesTEC-1, N (%) 165 (100%)	Physician's Choice Cohort, N (%)248 (100%)	SMD
Refractory status[1]	Penta refractory[2]	50 (30.3)	44 (17.7)	0.406
	Quad refractory[3]	58 (35.2)	80 (32.3)	
	Triple refractory[4]	20 (12.1)	59 (23.8)	
	≤ Double refractory	37 (22.4)	65 (26.2)	
ISS stage	I	88 (53.3)	85 (34.3)	0.566
	II	57 (34.5)	80 (32.3)	
	III	20 (12.1)	83 (33.5)	
Time to progression on last regimen	< 3 months	50 (30.3)	59 (23.8)	0.147
	≥ 3 months	115 (69.7)	189 (76.2)	
Extramedullary plasmacytoma[5]	No	137 (83)	215 (86.7)	0.102
	Yes	28 (17)	33 (13.3)	
Number of prior lines of treatment	≤ 4	78 (47.3)	126 (50.8)	0.071
	> 4	87 (52.7)	122 (49.2)	
Years since MM diagnosis	< 6	82 (49.7)	119 (48.0)	0.034
	≥ 6	83 (50.3)	129 (52.0)	
Average duration of prior lines of treatment	< 10 months	41 (24.8)	56 (22.6)	0.122
	10-14 months	51 (30.9)	66 (26.6)	
	≥ 15 months	73 (44.2)	126 (50.8)	
Age	< 65	86 (52.1)	88 (35.5)	0.340
	≥ 65	79 (47.9)	160 (64.5)	
Hemoglobin (g/dL)	< 12	124 (75.2)	181 (73)	0.050
	≥ 12	41 (24.8)	67 (27)	
LDH levels (units/L)	< 280	123 (74.5)	178 (71.8)	0.063
	≥ 280	42 (25.5)	70 (28.2)	
Creatinine Clearance (mL/min)	<60	44 (26.7)	100 (40.3)	0.285
	60 to <90	73 (44.2)	84 (33.9)	
	≥90	48 (29.1)	64 (25.8)	
ECOG status	0	55 (33.3)	65 (26.2)	0.156
	1	110 (66.7)	183 (73.8)	

Sex	Female	69 (41.8)	113 (45.6)	0.076
	Male	96 (58.2)	135 (54.4)	
Type of MM	IgG	91 (55.2)	103 (41.5)	0.275
	Non-IgG	74 (44.8)	145 (58.5)	
Prior stem cell transplant	No	30 (18.2)	88 (35.5)	0.398
	Yes	135 (81.8)	160 (64.5)	
Race[6]	White	134 (81.2)	182 (73.4)	0.188
	Other/Not reported	31 (18.8)	66 (26.6)	
Cytogenetic profile	High risk[7]	38 (23.0)	74 (29.8)	0.834
	Standard Risk	110 (66.7)	80 (32.3)	
	Missing	17 (10.3)	94 (37.9)	

[1] Refractoriness was defined as from the case report form as progressive disease/relapse (physician's choice cohort) and by International Myeloma Working Group consensus criteria (MajesTEC-1) [68].
[2] Refractory to at least two IMiDs, two PIs, and an anti-CD38 MoAB.
[3] Refractory to two IMiDs and two PIs.
[4] Refractory to two IMiDs and one PI; or two PIs and one IMiD
[5]Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas [128].
[6] Race in LocoMMotion was further categorized: 182 patients were white, 5 patients were black, 3 were categorized as 'Other', and race was not reported for 58 remaining patients.
[7] At least one of del17p, t(14;16), or t(4;14).
Abbreviations: dL, deciliter; ECOG, Eastern Cooperative Oncology Group; g, grams; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intention-to-treat; L, liters; LDH, lactate dehydrogenase; min, minutes; mL, milliliters; MM, multiple myeloma; MoAB, monoclonal antibody; PI, proteasome inhibitor; SMD, standardized mean difference
Small Difference (SMD 0.0 to 0.1)
Moderate Difference (SMD > 0.1 to 0.2)
Substantial Difference (SMD >0.2)

The scenario analysis showed a reduction in mean SMDs (i.e., an improvement in balance, on average) when incrementally including additional factors in the weighting of observations. The sensitivity analysis including variables with missing data showed a further improvement in the overall balance, with a reduced mean SMD of 0.062.

A visual presentation of the SMDs before weighting (unadjusted) and after weighting (adjusted) from Table 75 is provided in Figure 53. The overall distributional balance of the covariates before and after weighting are shown in Figure 51.

Table 75. Overview of Group Demographic Balance Before and After Weighting

	Categories	Before ATT Weighting (ITT)			After ATT Weighting (ITT); Main Analysis		After ATT Weighting (ITT); Sensitivity Analysis Incl. Variables with Missing Data	
		MajesTEC-1, N (%) 165 (100%)	Physician's Choice Cohort, NOBS (%) 248 (100%)	SMD	Physician's Choice Cohort, Weighted N (%)248 (100%)	SMD	Physician's Choice Cohort, Weighted N (%)248 (100%)	SMD
Refractory status[1]	≤ Double refractory	37 (22.4)	65 (26.2)	0.406	56 (22.5)	0.139	61 (24.5)	0.222
	Triple Refractory[2]	20 (12.1)	59 (23.8)		31 (12.4)		34 (13.6)	
	Quad refractory[3]	58 (35.2)	80 (32.3)		72 (29.2)		62 (25.0)	
	Penta refractory[4]	50 (30.3)	44 (17.7)		89 (35.8)		92 (36.9)	
ISS stage	I	88 (53.3)	85 (34.3)	0.566	135 (54.3)	0.022	129 (51.9)	0.022
	II	57 (34.5)	80 (32.3)		84 (33.7)		89 (36.0)	
	III	20 (12.1)	83 (33.5)		30 (11.9)		30 (12.2)	
Time to progression on last regimen	< 3 months	50 (30.3)	59 (23.8)	0.147	81 (32.6)	0.050	82 (33.1)	0.061
	≥ 3 months	115 (69.7)	189 (76.2)		167 (67.4)		166 (66.9)	
Extramedullary plasmacytoma5	Yes	28 (17.0)	33 (13.3)	0.102	43 (17.4)	0.010	43 (17.4)	0.011
	No	137 (83.0)	215 (86.7)		205 (82.6)		205 (82.6)	
Number of prior lines of treatment	≤ 4	78 (47.3)	126 (50.8)	0.071	109 (44.0)	0.067	114 (45.8)	0.029
	> 4	87 (52.7)	122 (49.2)		139 (56.0)		134 (54.2)	
Years since MM diagnosis	<6	82 (49.7)	119 (48.0)	0.034	114 (45.8)	0.077	125 (50.2)	0.011
	≥ 6	83 (50.3)	129 (52.0)		134 (54.2)		123 (49.8)	
Average Duration of Prior Lines (months)	< 10	41 (24.8)	56 (22.6)	0.122	62 (25.1)	0.047	65 (26.3)	0.089
	10-14	51 (30.9)	66 (26.6)		72 (29.2)		68 (27.5)	
	≥ 15	73 (44.2)	126 (50.8)		113 (45.7)		115 (46.3)	
Age	< 65	86 (52.1)	88 (35.5)	0.340	133 (53.6)	0.031	122 (49.2)	0.059
	≥ 65	79 (47.9)	160 (64.5)		115 (46.4)		126 (50.8)	
Hemoglobin (g/dL)	< 12	124 (75.2)	181 (73.0)	0.050	191 (77.1)	0.045	188 (75.8)	0.015
	≥ 12	41 (24.8)	67 (27.0)		57 (22.9)		60 (24.2)	
LDH levels (units/L)	< 280	123 (74.5)	178 (71.8)	0.063	186 (75.1)	0.012	189 (76.0)	0.035
	≥ 280	42 (25.5)	70 (28.2)		62 (24.9)		59 (24.0)	
Creatinine Clearance	<60	44 (26.7)	100 (40.3)	0.285	67 (26.9)	0.048	71 (28.7)	0.070
	60 to <90	73 (44.2)	84 (33.9)		104 (41.9)		111 (44.9)	
	≥ 90	48 (29.1)	64 (25.8)		77 (31.2)		66 (26.5)	
ECOG status	0	55 (33.3)	65 (26.2)	0.156	81 (32.6)	0.017	77 (30.9)	0.052
	1	110 (66.7)	183 (73.8)		167 (67.4)		171 (69.1)	
Sex	Male	96 (58.2)	135 (54.4)	0.076	134 (54.2)	0.081	123 (49.5)	0.174
	Female	69 (41.8)	113 (45.6)		114 (45.8)		125 (50.5)	

Type of MM	IgG	91 (55.2)	103 (41.5)	0.275	142 (57.4)	0.045	145 (58.5)	0.067
	Non-IgG	74 (44.8)	145 (58.5)		106 (42.6)		103 (41.5)	
Prior stem cell transplant	Yes	135 (81.8)	160 (64.5)	0.398	205 (82.7)	0.024	206 (83.0)	0.032
	No	30 (18.2)	88 (35.5)		43 (17.3)		42 (17.0)	
Summary Diagnostics – Main analyses								
Mean SMD		0.206			0.048		-	
Percentage of SMDs > 0.1		67%			7%		-	
Percentage of SMDs > 0.2		40%			0%		-	
Race[6]	White	134 (81.2)	182 (73.4)	0.188	181 (72.9)	0.200	206 (83.2)	0.052
	Other/Not Reported	31 (18.8)	66 (26.6)		67 (27.1)		42 (16.8)	
Cytogenetic risk	Standard Risk	110 (66.7)	80 (32.3)	0.834	78 (31.4)	0.835	161 (64.7)	0.045
	High Risk7	38 (23.0)	74 (29.8)		81 (32.6)		59 (23.7)	
	Missing	17 (10.3)	94 (37.9)		89 (36.1)		29 (11.5)	
Summary Diagnostics – Sensitivity analyses including variables with missingness								
Mean SMD		0.242			0.103		0.062	
Percentage of SMDs > 0.1		71%			18%		12%	
Percentage of SMDs > 0.2		41%			6%		6%	

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 treatment, years since MM diagnosis, average duration of prior lines, age, hemoglobin level, LDH level, creatinine clearance, ECOG status, sex, type of MM, and prior stem cell transplant. The sensitivity analysis including variables with missing data adjusted for all variables in the main analysis, plus race, and cytogenetic profile.

[1] Refractoriness was defined as from the case report form as progressive disease/relapse (physician's choice cohort) and by International Myeloma Working Group consensus criteria (MajesTEC-1) [68].

[2] Refractory to two IMiDs and one PI; or two PIs and one IMiD

[3] Refractory two IMiDs and two PIs.

[4] Refractory to at least two IMiDs, two PIs, and an anti-CD38 MoAB.

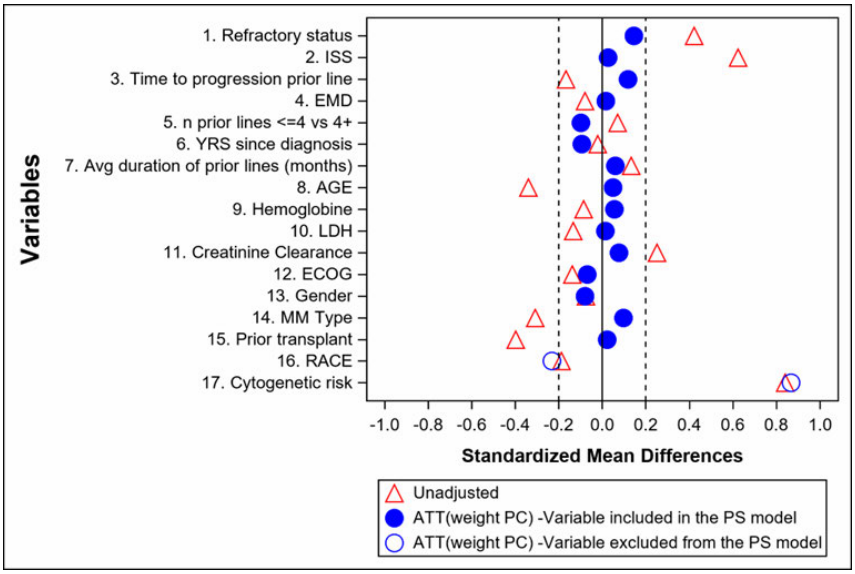
[5] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas [128].

[6] Race in LocoMMotion was further categorized: 182 patients were white, 5 patients were black, 3 were categorized as 'Other', and race was not reported for 58 remaining patients.

[7] At least one of del17p. t(14;16). or t(4;14).

Abbreviations: ATT, average treatment effect in the treated; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IMID, immunomodulatory drug; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MM, multiple myeloma; MoAB; monoclonal antibody; NOBS, number of observations; PI, proteasome inhibitor; SMD, standardized mean diffe

Figure 53. Balance of Covariates Before and After ATT Weighting in the ITT Population for the Main Analysis



Main analysis adjusted for refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of prior lines of treatment, years since MM diagnosis, average duration of prior lines, age, hemoglobin levels, LDH levels, creatinine clearance, ECOG status, sex, type of MM, and prior stem cell transplant. The sensitivity analysis including variables with missing data adjusted for all variables in the main analysis, plus race, and cytogenetic profile.
Abbreviations: ATT, average treatment effect in the treated; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MM, multiple myeloma; PC, physician's choice

19. Appendix G Extrapolation

19.1 Time to treatment discontinuation (TTD)

[redacted]

Table 76. Goodness-of-fit statistics for the different survival models for time to treatment discontinuation for teclistamab and PC

[redacted]

[redacted]

Figure 54. The best fitting distributions for time to treatment discontinuation in the teclistamab arm, overlayed with the PFS lognormal survival model

[redacted]

Abbreviations: TTD=Time to treatment discontinuation

[redacted]

[redacted]

Figure 55. The two best fitting distributions overlayed on the PFS model of lognormal for time to treatment discontinuation in the physician's choice arm

Abbreviations: TTD=Time to treatment discontinuation, PFS=Progression free survival.

19.2 Administration Frequency Switch (AFS)

[redacted]

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Figure 56. All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (one-year time-horizon).

Figure 57. All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (two-year time-horizon).

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Figure 58 All models overlayed on the Kaplan-Meier estimate for administration frequency switchprogression free survival in the teclistamab arm (40-year time-horizon).

AIC and BIC scores for the different survival models for teclistamab are presented in Table 77.

Table **77. Goodness-of-fit statistics for the different survival models for administration frequency switch for teclistamab**

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Figure 59. AFS base case (Teclistamab).

20. Appendix H Literature search for HRQoL data

A systematic literature was not the basis for selection of HRQoL data.

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21. Appendix I Mapping of HRQoL data

See section 8.4

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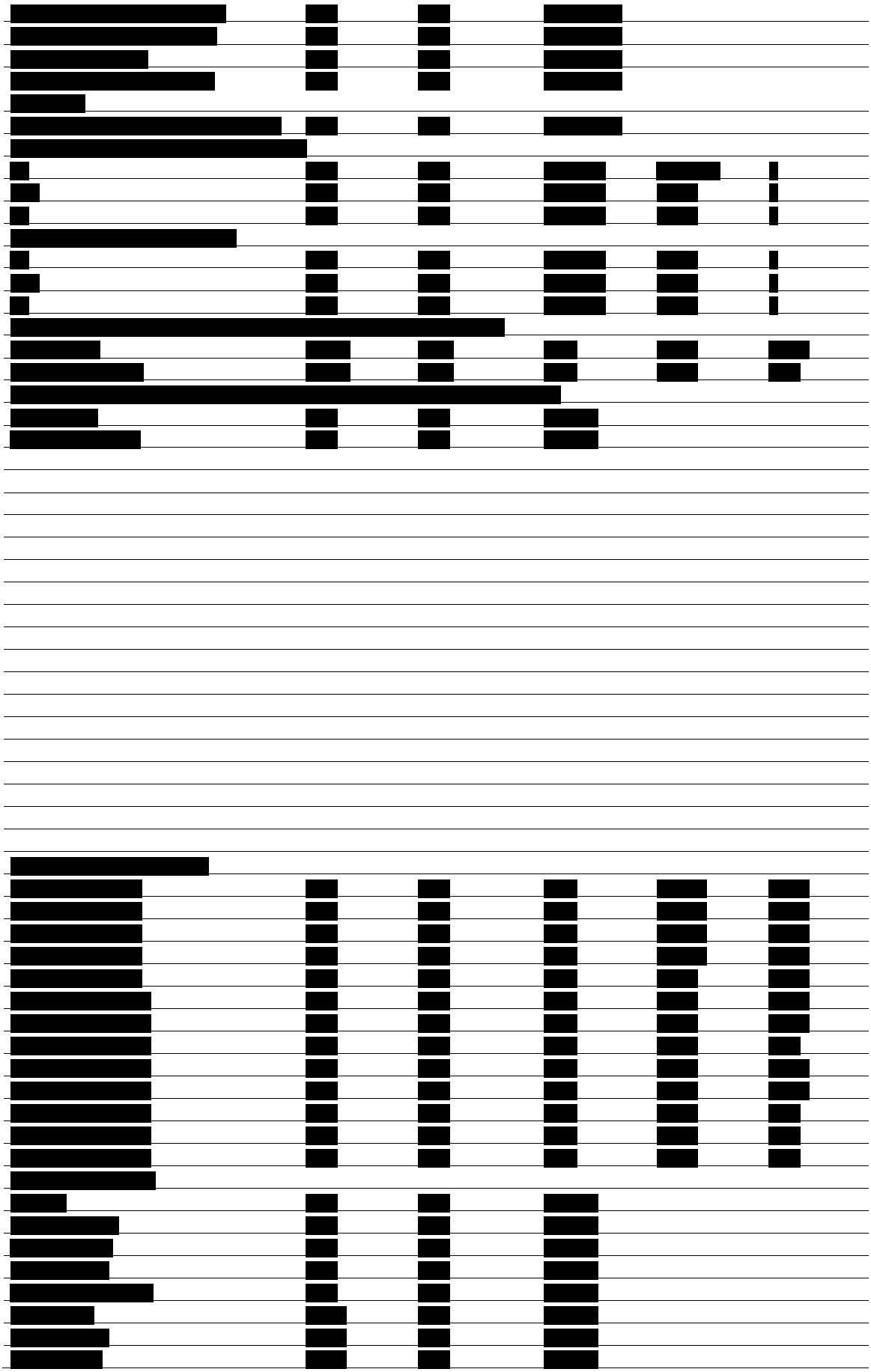
22. Appendix J Probabilistic sensitivity analyses

[redacted]

Table 78. Assumptions applied for probabilistic sensitivity analysis

[redacted]



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[redacted]

* b is a random value drawn from the Dirichlet distribution.

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23. Appendix K Patient reported outcomes

23.1 MajesTEC-1

Table 79. Number of patients complying withith EQ-5D-5L Assessment Over Time During Treatment during PFS (Phase 2 Cohort A; All Treated Analysis (January 2023 data cut))

	N*
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

Table 80. Compliance with EORTC-QLQ-C30 Assessment Over Time During Treatment (Phase 2 Cohort A; all treated analysis set (January 2023 datacut)

	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]

[redacted]

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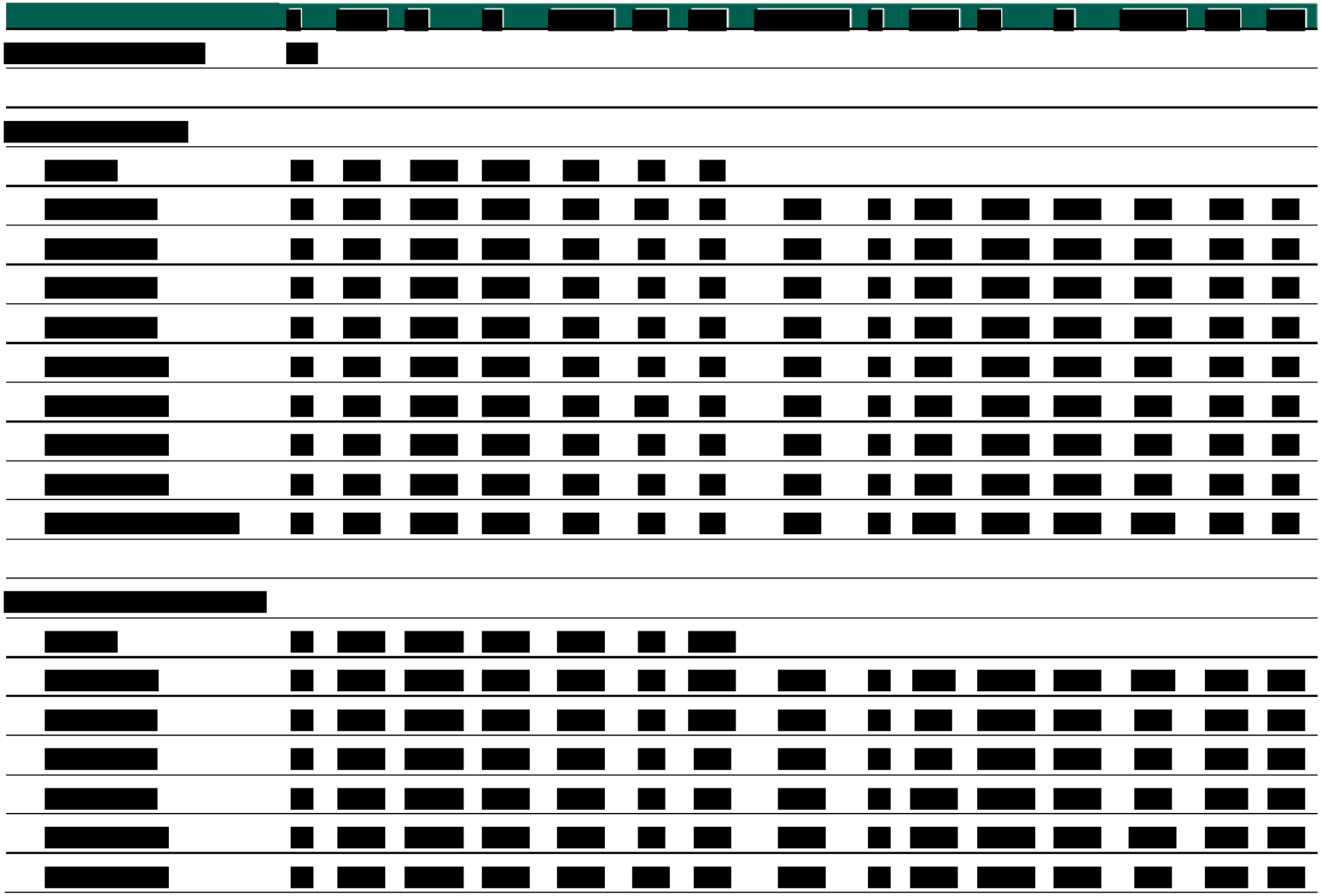
Table 81. Summary of EQ-5D-5L Assessment and Change From Baseline Over Time in utility score and VAS, (Phase 2 Cohort A; All Treated Analysis Set)



	N	Mean	SD	SE	Median	Min	Max	Base Mean	N	Mean	SD	SE	Median	Min	Max
[redacted]															
[redacted]															
[redacted]															

[redacted]

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Table 82. Summary of EORTC-QLQ-C30 Assessment and Change From Baseline Over Time (Phase 2 Cohort A)

	Measured Value							Change From Baseline							
	N	Mean	SD	SE	Median	Min	Max	Base Mean	N	Mean	SD	SE	Median	Min	Max
[redacted]	[redacted]														
[redacted]															
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]								
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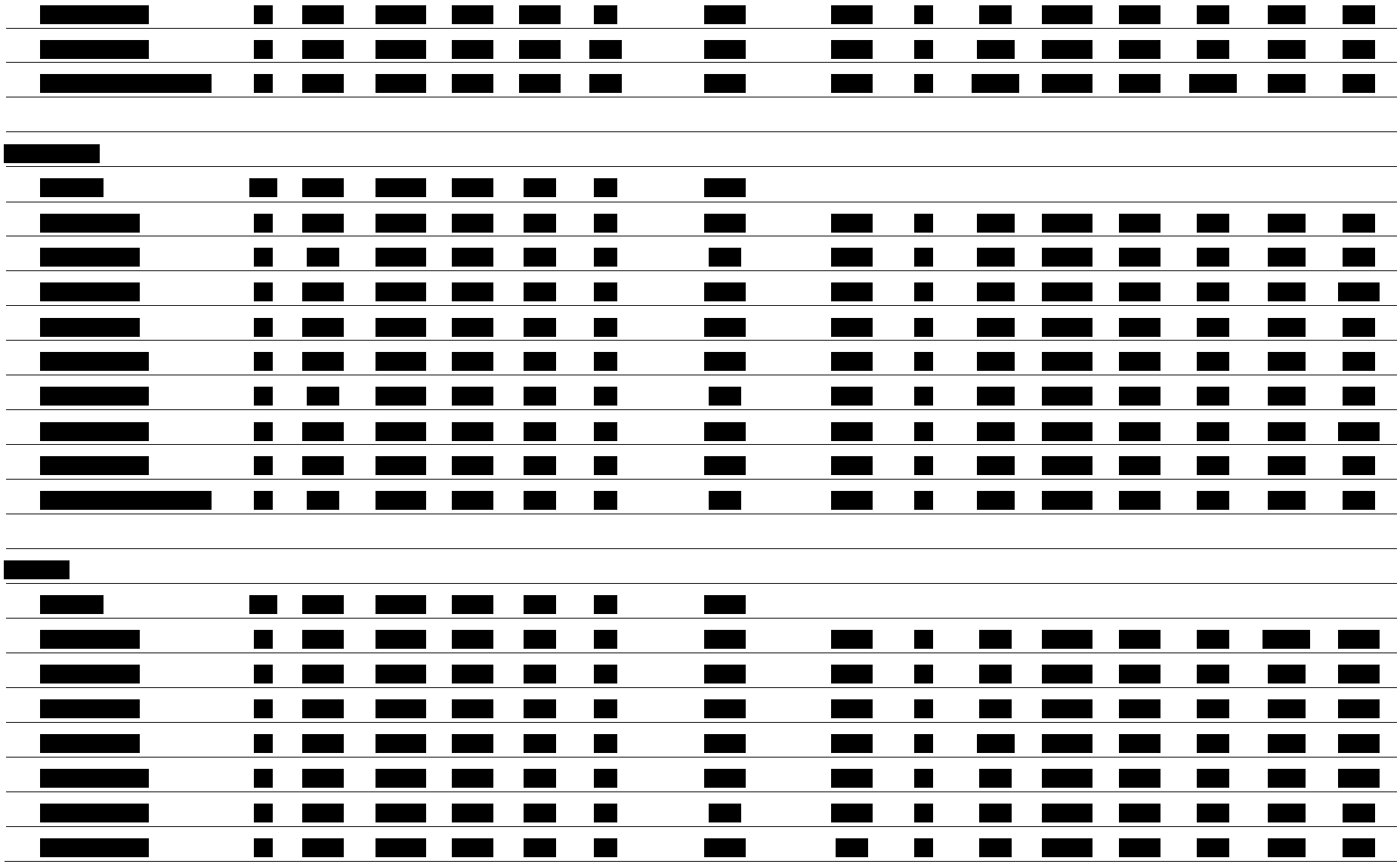

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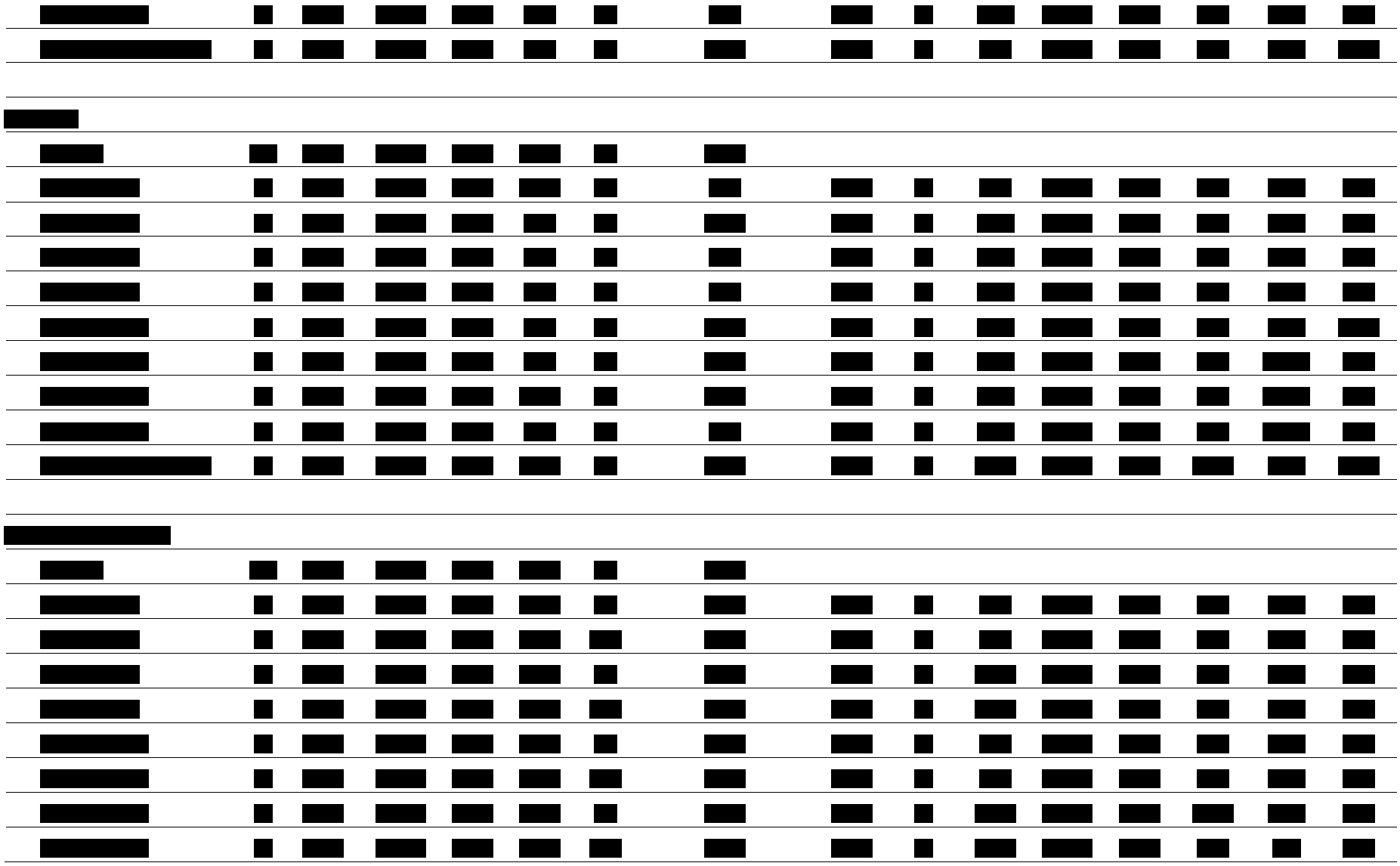

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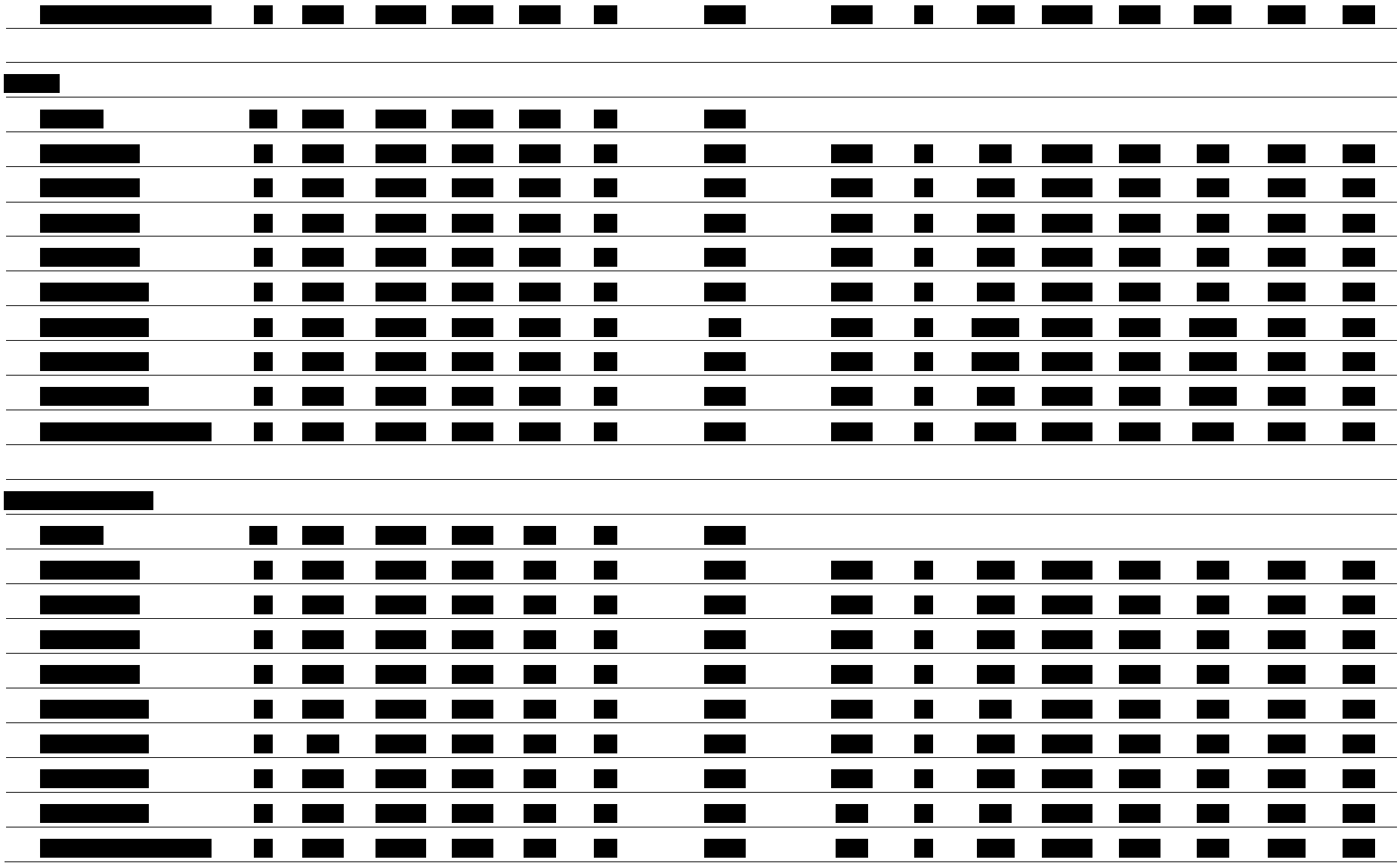

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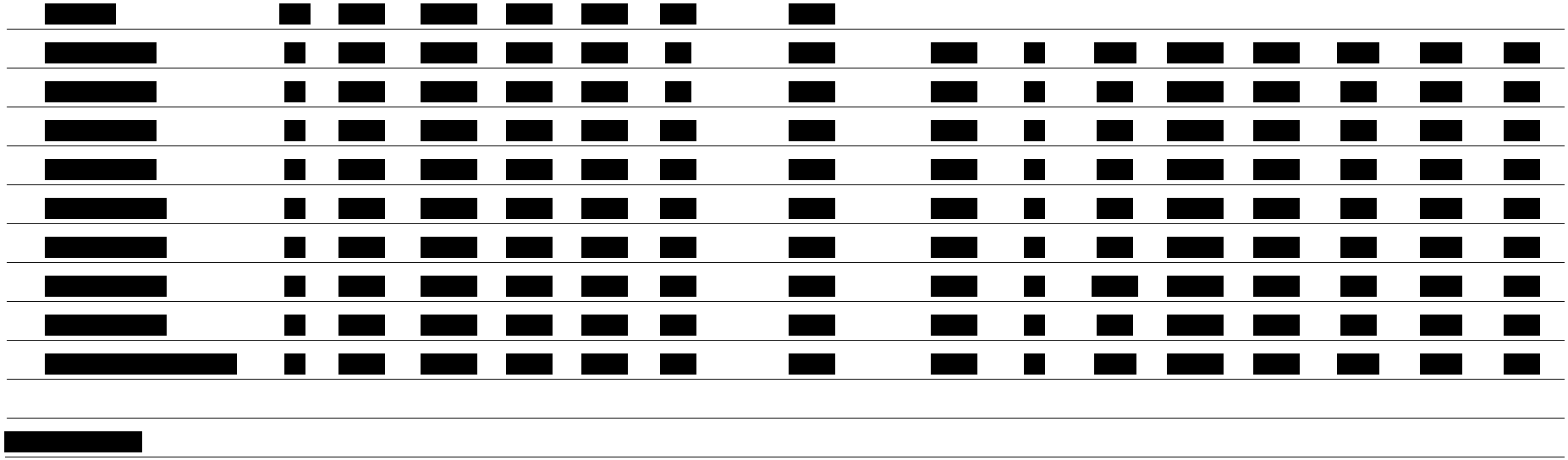

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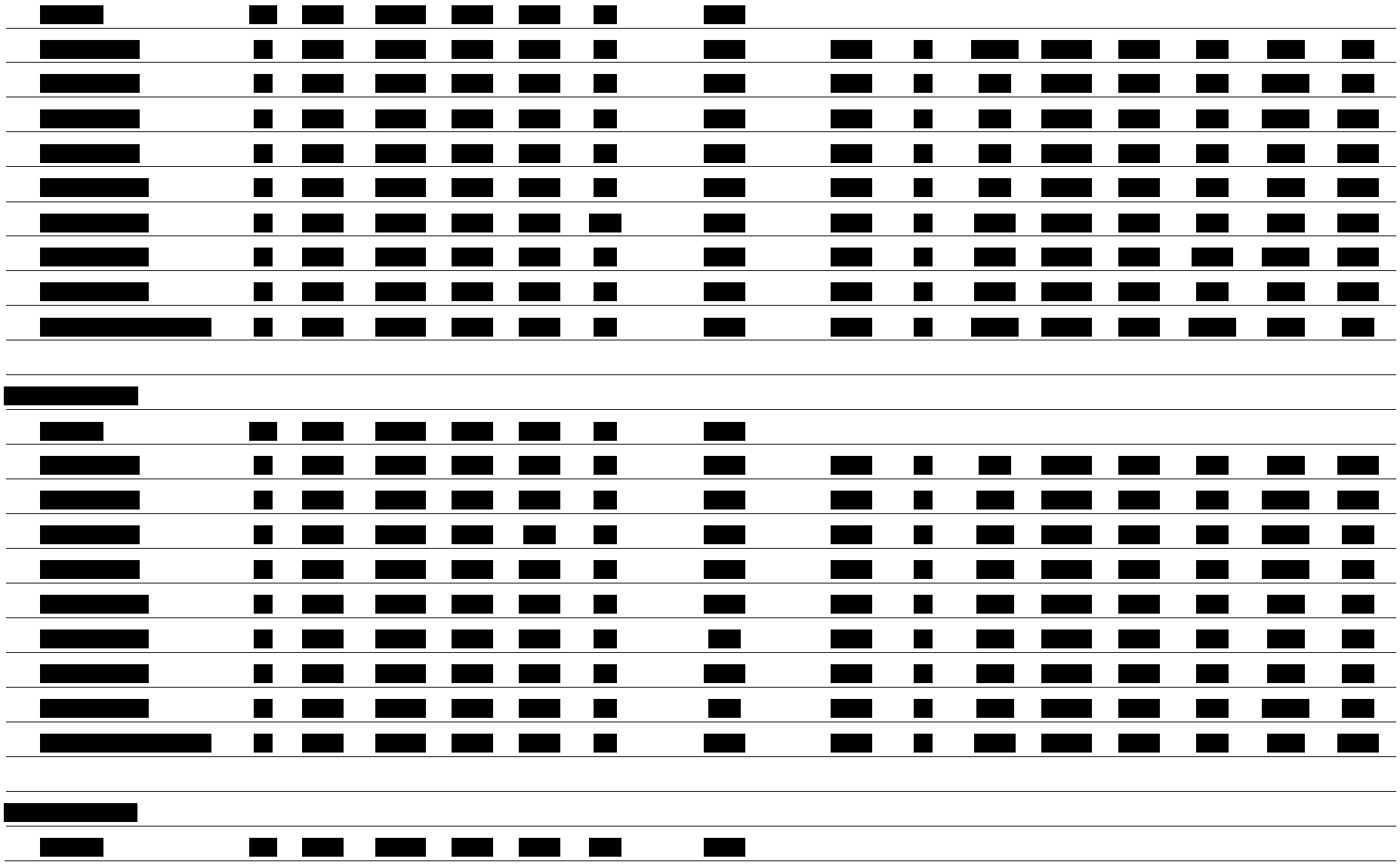

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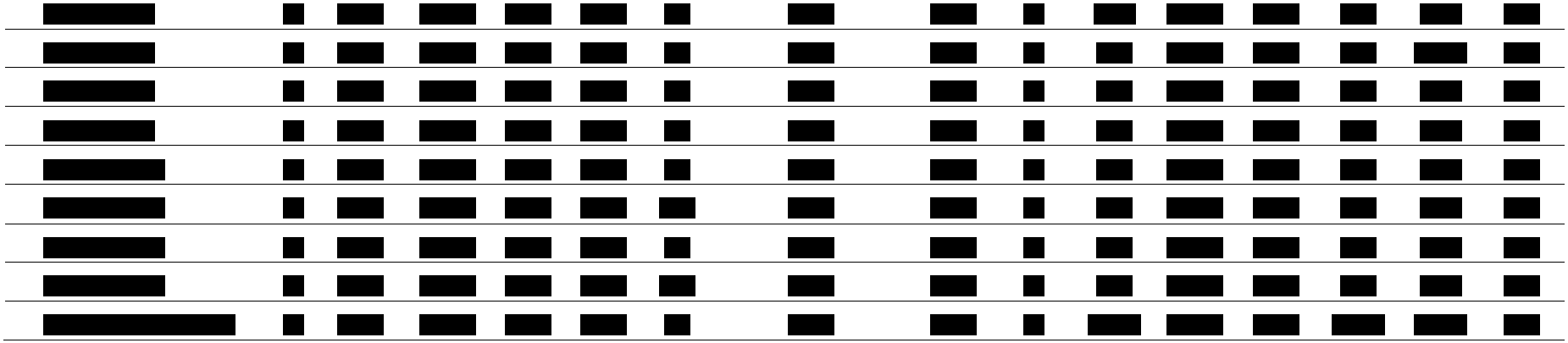

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23.2 LocoMMotion

Table 83. Summary of Compliance for PRO Assessments; All Treated Analysis Set

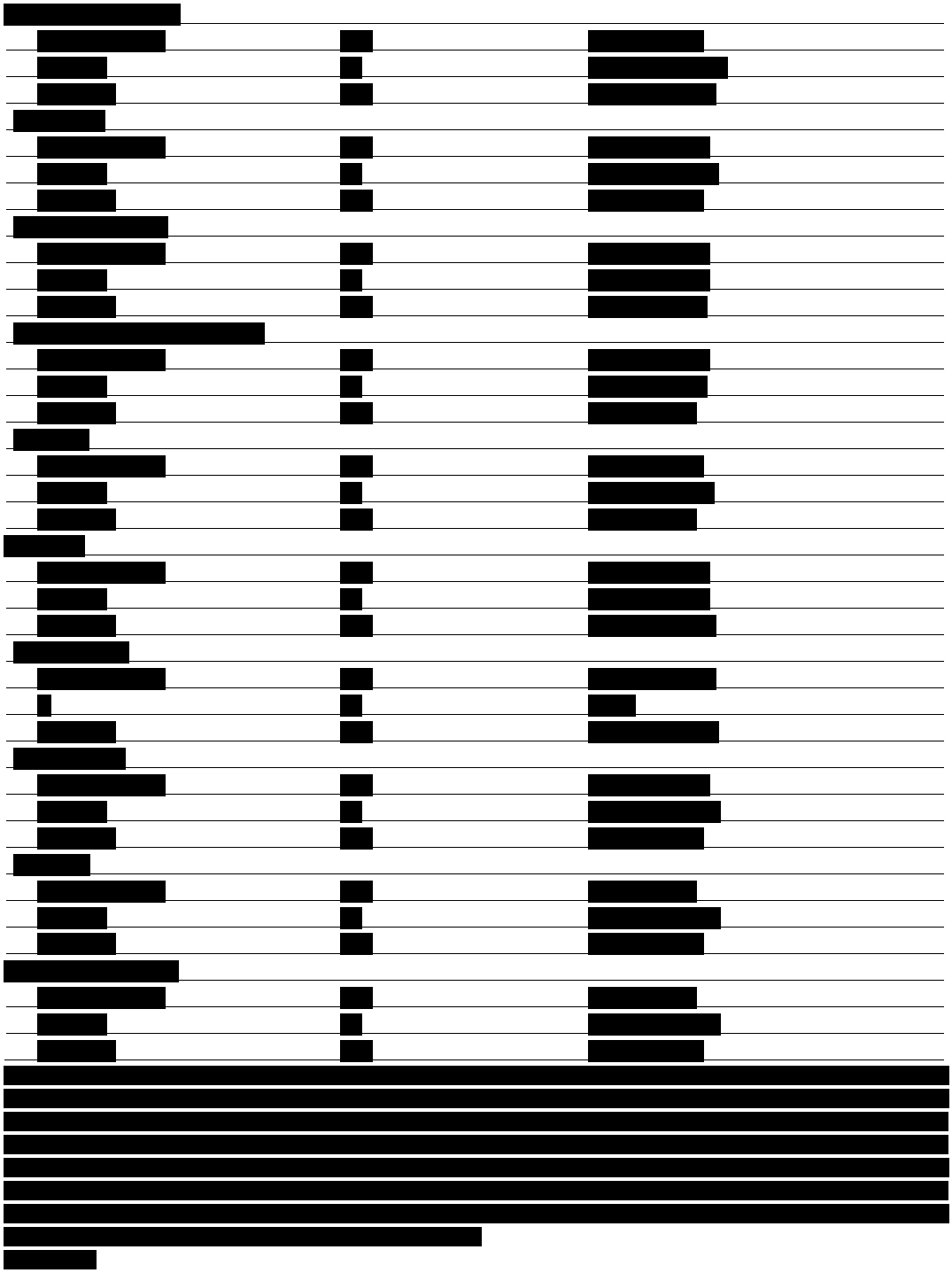
	n	Mean Percent Compliance (95% CI)
[redacted]		

Table 84. Summary of Change from Baseline in EQ-5D-5L: Mixed Model for Repeated Measures; All Treated Analysis Set

	n	LS Means of Change from Baseline (95% CI)
[redacted]		

Table 85. Summary of Change from Baseline in EORTC QLQ-C30 Assessments: Mixed Model for Repeated Measures; All Treated Analysis

n=248	n	LS Means of Change from Baseline (95% CI)
[redacted]		



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