Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Johnson & Johnson Innovative Medicine:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Further response to question C2

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK
   b. Royal College of Pathologists

4. **Expert personal perspectives** from:
   a. Dr Neil Rabin - clinical expert, nominated by Johnson and Johnson Innovative Medicine
   b. Dr Sarah Lawless – clinical expert, nominated by the UK Myeloma Society
   c. Caroline Donaghue – patient expert, nominated by Myeloma UK
   d. Ms Sue Harley – patient expert, nominated by Myeloma UK

5. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science (BCEIS)
   a. External Assessment Report
   b. Appendix: The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool
   c. Appendix: IVIG CCG policy

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID5082]

Company evidence submission

March 2025

File name	Version	Contains confidential information	Date
ID5082_Talquetamab in TCE RRMM_Evidence Submission_290725 [noCON]_UPDATE	FINAL2	Yes	29th July 2025

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Abbreviations

Acronym	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Average effect of treatment in control group

ATE	Average treatment effect
ATO	Average treatment effect on the overlap population
ATT	Average treatment effect on the treated
BCMA	B cell maturation antigen
BelBorDex	Belantamab mafodotin plus bortezomib and dexamethasone
BelPomDex	Belantamab mafodotin plus pomalidomide and dexamethasone
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BsAb	Bispecific antibodies
BSH	British Society for Haematology
CAR-T	Chimeric antigen receptor-T cell
CD	Cluster of differentiation
CDF	Cancer Drugs Fund
CELMoD	Cereblon E3 ligase modulatory drug
CEM	Cost-effectiveness model
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRAB	Calcium levels, renal impairment, anaemia and bone disease
CRS	Cytokine release syndrome
CSR	Clinical study report
DCO	Data cut-off
DLT	Dose limiting toxicity
DoR	Duration of response
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	External Assessment Group
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EHA	European Haematology Association
EMA	European Medicines Agency
EMD	Extramedullary plasmacytoma
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire
EQ-5D	EuroQol Five Dimensions Five Level Questionnaire
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FLC	Free light chain
GCP	Good Clinical Practice

GPRC5D	G protein-coupled receptor class 5D
HDT	High dose therapy
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health and Safety Executive
HSUV	Health state utility value
HTA	Health Technology Appraisal
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost effectiveness ratio
ICF	Informed consent form
ICU	Intensive care unit
Ig	Immunoglobulin
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
INHB	Incremental net health benefit.
IPD	Individual patient data
IPTW	Inverse probability of treatment
IRC	Independent review committee
IRR	Infusion-related reaction
IsaPomDex	Isatuximab with pomalidomide and dexamethasone
IxaLenDex	Ixazomib plus lenalidomide plus dexamethasone
ISS	International Staging System
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LOT	Line of treatment
LYG	Life years gained
mAb	Monoclonal antibody
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly index of medical specialities
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
MyPOS	Myeloma Patient Outcome Scale
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NE	Not estimable
NGS	Next generation sequencing

NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PanBorDex	Panobinostat plus bortezomib and dexamethasone
PAR	Public assessment report
PAS	Patient access scheme
PD	Progressed disease
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PH	Proportional hazard
PI	Proteasome inhibitor
PICO	Patient, intervention, comparison, outcome
PomDex	Pomalidomide plus dexamethasone
PP	Post-progression
PPS	Post-progression survival
PRO	Patient reported outcome
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses
PS	Propensity score
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality adjusted life year
Q2W	Biweekly
QW	Weekly
RP2D	Recommended phase 2 dose
RR	Relative risk
RRMM	Relapsed and refractory multiple myeloma
RWE	Real-world evidence
SAE	Serious adverse event
SC	Subcutaneous
SCHARR	Sheffield Centre for Health and Related Research
sCR	Stringent complete response
SD	Standard deviation
SE	Standard error
SelDex	Selinexor plus dexamethasone
SIQOL	Single-item quality of life
SLR	Systematic literature review

SMD	Standardised mean differences
SMM	Smouldering multiple myeloma
SmPC	Summary of product characteristics
SoC	Standard of care
SPM	Second primary malignancy
TA	Technology appraisal
TAL	Talquetamab
TCE	Triple-class exposed
TCR	T-cell receptor
TEAE	Treatment emergent adverse event
TEC	Teclistamab
TLS	Tumor lysis syndrome
ToT	Time on treatment
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTR	Time to response
VGPR	Very good partial response
WTP	Willingness-to-pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

This submission is aligned with the marketing authorisation of talquetamab, for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody (mAb) and have demonstrated disease progression on their last therapy (hereafter referred to as 'triple-class exposed [TCE] patients').[1]

The advent and availability of BCMA-targeting T cell receptor (TCR) bispecific antibody (BsAb) therapies represented a step-change in the treatment of TCE RRMM. Amongst them is teclistamab, which is currently the only licensed and routinely reimbursed TCR BsAb in England and Wales in the fourth-line and beyond (4L+) treatment setting.[2,3] Advice from UK clinical experts indicates that BCMA-targeted BsAb therapies will now be used preferentially versus the previous standard of care (SoC) regimens including pomalidomide plus dexamethasone (PomDex), panobinostat plus bortezomib and dexamethasone (PanBorDex) and selinexor plus dexamethasone (SelDex). The evidence presented within the recent appraisal of teclistamab [TA1015] demonstrated that it is associated with significant clinical, heath-related quality of life (HRQoL) and economic benefits versus these treatments.[3] Therefore, for the purposes of decision making, teclistamab represents the most relevant comparator to talquetamab in this submission.

The population of TCE RRMM patients with prior TCR exposure

The Company acknowledges that in the UK there is likely to be an emerging group of patients receiving teclistamab (or elranatamab [ID4026] another TCR BsAb therapy, funded via the Cancer Drugs Fund [CDF]) who experience disease progression and require subsequent treatments, henceforth referred to as the 'TCR-exposed' population.[3-6] However, due to the recency of the recommendations for both teclistamab (November 2024) and elranatamab (December 2024, via the CDF), the population of TCR-exposed patients in UK clinical practice is currently very small, which is consistent with the orphan designation status of talquetamab in this indication.[3, 7, 8]

Given that the evidence base in fifth-line and beyond (5L+) TCR exposed patients remains limited due to the rarity of the condition;[9] and the aforementioned benefits of teclistamab over the previous SoC treatment options available to TCR-exposed patients, this submission takes a pragmatic approach in which demonstration of clinical- and cost-effectiveness of talquetamab versus teclistamab will, by extension, demonstrate clinical- and cost-effectiveness of talquetamab versus PomDex, PanBorDex and SelDex.

An overview of the decision problem addressed within this submission compared to the final scope issued by NICE, is summarised in Table 1.[10]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. If the evidence allows, the following subgroups will be considered: • Prior T-cell redirection therapy • Prior lines of therapy	Adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	Evidence provided in the recent NICE appraisal of teclistamab demonstrated that teclistamab is associated with significant clinical benefits and is cost-effective against previous SoC (PomDex, PanBorDex and SelDex).[3] Teclistamab is therefore anticipated to be used preferentially over these treatments in TCE RRMM patients in the 4L+ setting in UK clinical practice, as supported by UK clinical experts. Due to the recency of the recommendations for both teclistamab (November 2024) and elranatamab (December 2024, via the CDF), the population of 5L+ TCR-exposed patients in UK clinical practice is currently very small. This is consistent with the orphan designation status of talquetamab in this indication.[7] Given that the evidence base in 5L+ TCR exposed patients remains limited due to the rarity of the condition;[9] and that teclistamab recently demonstrated clinical and cost-effectiveness benefits against the previous SoC treatment options available to TCR-exposed patients, the evidence does not permit the consideration of the subgroups based on prior T cell redirection therapy or prior lines of therapy.
Intervention	Talquetamab	Talquetamab	N/A
Comparator(s)	• Panobinostat plus bortezomib and dexamethasone (PanBorDex)	Teclistamab	The Company considers teclistamab [TA1015] to be the most relevant comparator for the purposes of decision making.[3]

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
	• Pomalidomide plus low-dose dexamethasone (PomDex) • Selinexor plus dexamethasone (SelDex) • Teclistamab • Isatuximab plus pomalidomide and dexamethasone (subject to NICE evaluation) • Belantamab mafodotin with pomalidomide and dexamethasone (subject to NICE evaluation) • Belantamab mafodotin with bortezomib and dexamethasone (subject to NICE evaluation)		Teclistamab was recently recommended by NICE for routine commissioning for the treatment of RRMM in adults, only after 3 or more lines of treatment (including an IMiD, PI, anti-CD38 mAb) when the myeloma has progressed on the last treatment.[3] Prior to the recommendation of teclistamab, it was established that *'the main treatment that is used for RRMM myeloma after 3 or more lines of treatment was PomDex. If PomDex was not suitable, PanBorDex could be used. Additionally, if the myeloma is refractory to 4 or more treatments (i.e., in the 5L+ setting) SelDex was used'*.[3] Teclistamab significantly improves clinical outcomes for patients compared to PomDex, PanBorDex and SelDex, and was accepted to be cost-effective against these treatment options.[3] Therefore, teclistamab is expected to be used preferentially over these treatments in TCE RRMM patients in 4L+ TCE RRMM patients, and is the most relevant comparator for this submission, a view that is also aligned with those of clinical experts. The Company does not consider the following treatments to be relevant comparators: • PomDex (TA427), PanBorDex (TA380) and SelDex (TA970) are anticipated to have been displaced by teclistamab as a new SoC for NHS patients with 4L+ TCE RRMM, owing to its

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
			aforementioned benefits over these treatments. • Isatuximab with pomalidomide and dexamethasone (IsaPomDex) is not used in the population under consideration. Real-world evidence in the UK has confirmed that over 95% of IsaPomDex patients are anti-CD38 naïve and therefore would not be eligible to receive talquetamab.[11] • Belantamab madofotin with bortezomib and dexamethasone (ID6212) and belantamab madofotin with pomalidomide and dexamethasone (ID6211) are not relevant comparators to talquetamab in this setting. Both of these treatments are pending NICE guidance and therefore, are not considered as established in clinical practice in the NHS at the time of writing this submission. Further detail regarding the choice of comparator is provided in Table 3, Section 1.3.4.

Outcomes	The outcome measured to be considered include:
	• Overall survival (OS)
	• Progression-free survival (PFS)
	• Response rates
	• Time to next treatment (TTNT)
		Outcomes included in this submission are:
		• OS
		• PFS
		• Response rates:
		  ○ Overall response rate (ORR)
		  ○ Disease response
		  ○ Duration of response
			The write-up of the patient-reported outcomes (PRO) data from the pivotal trial informing the clinical effectiveness data for talquetamab (i.e., MonumenTAL-1) was not available in time for the submission deadline and therefore will not be presented. This data will be provided as an addendum when possible.

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
	• Adverse effects (AEs) of treatment • Health-related quality-of-life (HRQoL)	○ Time to response • Time to treatment discontinuation (TTD) • TTNT • AEs • Other: ○ Minimal residual disease (MRD) negativity rate	However, as mentioned in Section 3.4.2, the EuroQoL Five Dimension Five Level Questionnaire (EQ-5D-5L) descriptive scores from MonumenTAL-1 (September 2024 data cut-off) were mapped onto the 3L UK value set to inform the economic model.

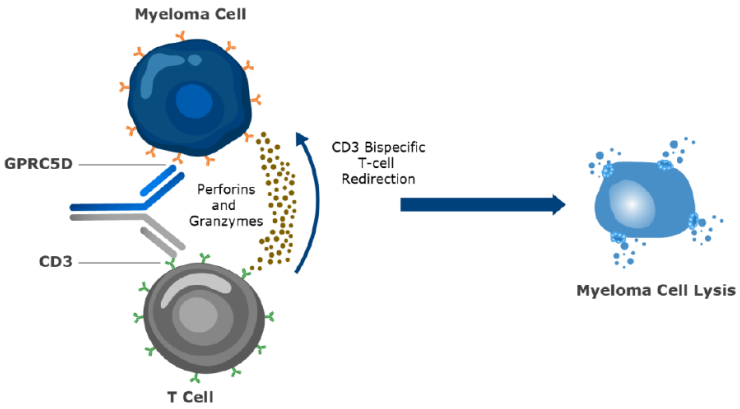
Abbreviations: 1L: first line; 4L+: fourth line and beyond; 5L+: fifth line and beyond; AEs: adverse events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item; EQ-5D-5L: EuroQol Five Dimension Five Level Questionnaire; HRQoL: health-related quality of life; IMiD: immunomodulatory drug; IsaPomDex: isatuximab plus pomalidomide plus dexamethasone; MM: multiple myeloma; MRD: minimal residual disease; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: overall response rate; OS: overall survival; PanBorDex: panobinostat plus bortezomib and dexamethasone; PFS: progression-free survival; PGIS: Patient Global Impression of Severity; PI: proteasome inhibitor; PomDex: pomalidomide plus low-dose dexamethasone; RRMM: relapsed or refractory multiple myeloma; RWE: real-world evidence; SelDex: selinexor plus dexamethasone; SoC: standard of care; TCE: triple-class exposed; TCR: T-cell redirecting therapy; TTD: time to discontinuation; TTNT: time to next treatment.

1.2 *Description of the technology being evaluated*

An overview of the technology being appraised, talquetamab, is presented in Table 2.

The summary of product characteristics (SmPC) and UK public assessment report (PAR) for talquetamab in the indication of relevance to this submission are provided in the reference pack accompanying this submission (see Appendix A).[1, 12]

Table 2: Technology being appraised

UK approved name and brand name	Talquetamab (Talvey®)
Mechanism of action	Talquetamab is a humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody that binds to cluster of differentiation (CD) 3 receptors expressed by T cells and G protein-coupled receptor class 5D (GPRC5D), a novel target expressed on the surface of malignant MM cells.[1] With its dual binding sites, talquetamab redirects patients' CD3+ T cells to GPRC5D-expressing tumour cells to kill them. Talquetamab targets MM cells preferentially, with minimal to no GPRC5D expression observed on B cells or their precursors (including hematopoietic stem cells and common lymphoid progenitors), meaning that off-target effects are minimised and immune function maintained.[1] Further information of the mechanism of action of talquetamab is presented in Section 1.3.4. **Figure 1: Mechanism of Action of Talquetamab**  **Abbreviations:** GPRC5D; G protein couple receptor class 5D; CD3: cluster of differentiation 3. **Source:** J&J IM. TALVEY Medical Information. (2024)[13]
Marketing authorisation/CE mark status	Talquetamab received orphan designation and marketing authorisation from the European Medicines Agency (EMA) on the 20th and 21st August 2023, respectively.[7,9] A UK licence for talquetamab was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 9th October 2023 via the European Commission (EC) Decision Reliance Procedure.[14]

Indications and any restriction(s) as described in the SmPC	The licensed indication for talquetamab is:[1] *"As a monotherapy for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy"*
Method of administration and dosage	Talquetamab is available as a 2mg/ml and a 40mg/ml solution for subcutaneous (SC) injection.[1] Treatment with talquetamab should be initiated and supervised by physicians experienced in the treatment of MM. Talquetamab should be administered subcutaneously on a weekly (0.4 mg/kg per dose) or biweekly (every 2 weeks [0.8 mg/kg per dose]) dosing schedule.[1] Clinical expert feedback received by the Company indicated that the majority (90%) of patients in UK clinical practice will likely receive the biweekly regimen, as it is associated with fewer hospital visits than the weekly regimen during the maintenance phase, therefore improving convenience (aligning with patient preference), and reducing healthcare resource requirements. This is aligned with a real-world evidence study (RealiTAL) which included 93 patients receiving talquetamab across seven European Countries, of which 88% of patients began their treatment on the biweekly dosing regimen.[15] Fewer hospital visits and reduced hospital burden are additional benefits that could address key unmet needs in TCE RRMM identified by clinical and patient experts.[16] Patients have also expressed the value they place on treatments that reduce the requirement to frequently attend hospital.[3] Details of the full dosing schedule for talquetamab, including the step-up dosing regimen, are provided in the SmPC.[1] Treatment with talquetamab should be continued until disease progression or unacceptable toxicity.[1]
Additional tests or investigations	Patients are instructed to remain within proximity of a healthcare facility and should be monitored for 48 hours after administration of all doses within the talquetamab step-up dosing schedule for signs and symptoms of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS).[1] The following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of talquetamab during the step-up phase to reduce the risk of CRS:[1] • Corticosteroid (oral or intravenous dexamethasone 16 mg or equivalent) • Antihistamine (oral or intravenous diphenhydramine 50 mg or equivalent) • Antipyretics (oral or intravenous paracetamol 650 mg to 1,000 mg or equivalent) Pre-treatment medicinal products should be administered prior to subsequent doses for patients who repeat doses within the

	talquetamab step-up phase due to dose delays or for patients who experienced CRS.[1] Prior to starting treatment with talquetamab, prophylaxis should be considered for the prevention of infections, per local institutional guidelines.[1] Dose delays or dose modifications may be required to manage toxicities related to talquetamab, the details of which can be found in the SmPC.[1] Pre-treatment medicinal products should be administered prior to restarting talquetamab, and patients should be monitored accordingly.[1]
List price and average cost of a course of treatment	The list price for available formulations of talquetamab are:[17] Talquetamab 2 mg/ml solution: £326.41 per vial Talquetamab 40 mg/ml solution: £4,352.00 per vial
Patient access scheme (if applicable)	This submission includes a confidential simple patient access scheme (PAS) for talquetamab, representing a discount to the list price of [redacted] The resulting with-PAS price of talquetamab is: Talquetamab 2 mg/ml solution: £[redacted] per vial Talquetamab 40 mg/ml solution: £[redacted] per vial

Abbreviations: BCMA: B cell maturation antigen; CD3: cluster of differentiation 3; CRS: cytokine release syndrome; EMA: European Medicines Agency; GPRC5D: G protein coupled receptor class 5D; ICANS: immune effector cell-associated neurotoxicity syndrome; IMiD: immunomodulatory agent; MHRA: Medicines and Healthcare Products Regulatory Agency; MM: multiple myeloma; PAS: patient access scheme; PI: proteasome inhibitor; SC: subcutaneous; SmPC: summary of product characteristics.
Sources: MHRA. SmPC for TALVEY. 2024.[1] J&J IM. TALVEY Medical Information. (2024).[13] EMA. Talvey (Talquetamab). 2023.[7] MHRA. Marketing authorisations granted 1 October 2023 to 14 October 2023. 2023.[14] BNF. Talquetamab Medicinal Forms. 2024.[17]

1.3 Health condition and position of the technology in the treatment pathway

Patients with TCE RRMM have relapsed on three previous lines of therapy, and face poor prognosis, alongside a substantial physical and psychological burden

- MM is a rare and predominantly incurable haematological cancer accounting for 2% of all new cancer cases as well as 2% of all cancer-related deaths in the UK. MM is associated with a substantial clinical burden, with patients often presenting with recurring or persistent infection, fatigue and unremitting bone pain.[18, 19]
- All patients will eventually relapse or fail to respond to each line of treatment, as MM progresses to RRMM.[20] Once patients have received treatment with a PI, IMiD and an anti-CD38 mAb, the condition is described as TCE RRMM.
- The progression of MM to RRMM intensifies the burden of disease, with patients with relapsed/progressive disease reporting more severe and more numerous symptoms than those with newly diagnosed or stable MM, coupled with high levels of emotional distress.[21, 22, 23]
- The symptom burden worsens with each line of therapy, which additionally translates to poor HRQoL.[24, 25] Of note, MM is associated with the lowest patient HRQoL of all haematological cancers.[26, 27]
- The burden of TCE RRMM extends beyond the patients themselves. The carers of patients with MM experience a high burden related to providing direct care, coordinating care and providing emotional support to patients. This is particularly true of the informal carers of TCE RRMM patients, who experience fear and anxiety over losing their loved one.[28, 29]

There remains an unmet need for non-BCMA targeting treatment options to personalise disease management while extending survival outcomes for TCE RRMM patients and reducing the risk of severe infections and infection-related mortality

- The recent approval of teclistamab, a BCMA-targeting bispecific therapy, represented a step-change in the treatment paradigm for TCE RRMM patients versus previous SoC (PomDex, PanBorDex and SelDex). Teclistamab therefore, now represents a new SoC in routine UK clinical practice. Despite this major advancement, TCE RRMM is still a terminal, end of life illness, with a median OS under 24 months. This reinforces the need for alternative options to further enhance life expectancy and to provide greater patient and clinician choice to personalise disease management.[3]
    - Providing patients with choice is a fundamental aspect of NHS care and service and is extremely important in giving patients an increased sense of control over the management of their disease.[30, 31]
- BCMA-targeting TCR therapies are associated with an increased risk of Grade 3/4 (severe or life threatening) infections due to off-target effects on patients' normal B cell and plasma cells compared to non-BCMA targeting therapies.[32-39]
    - A proportion of patients ([redacted]%) experienced Grade 3/4 infections in MajesTEC-1, the pivotal trial which informed the teclistamab appraisal [TA1015].[3, 40]
    - Consequently, patients require treatment with IVIg to mitigate the infection-related morbidities as reflected in the proportion of IVIg use ([redacted]%) in MajesTEC-1.[40]
    - Infection-related mortality also represents a key concern to patients and clinicians, with infection-related deaths constituting [redacted]% of all deaths in patients receiving teclistamab in MajesTEC-1.[40]
    - Clinical insights from UK experts concluded that an unmet need exists for TCE RRMM treatments with alternative targets that are associated with a lower risk of severe infections, which can in turn reduce the impact of infections on both patients' QoL and the NHS resources via reduced need for IVIg administration.[16]

- The QoL burden associated with TCE RRMM is further increased by the fact that all MM treatments routinely reimbursed by NICE in the relapsed setting, apart from teclistamab, require concomitant treatment with the corticosteroid dexamethasone. Dexamethasone is associated with high levels of toxicity and therefore has a significant impact on the daily lives of patients.[41]
- Patients have also expressed a desire for treatments with a flexible dosing regimen that does not require them to attend hospital so frequently, an unmet need that is further supported by clinical opinion.[3, 16]

By targeting G protein receptor class 5D (GPRC5D), talquetamab presents a compelling alternative option to teclistamab for 4L+ TCE RRMM patients, that provides incremental survival gains and an improved infection-related safety profile. Similar to teclistamab, talquetamab is a dexamethasone-free regimen, thereby alleviating the detrimental impact of steroids on patient QoL and persevering QoL benefits.

- Talquetamab is a first-in-class, humanised IgG4- PAA TCR BsAb that binds to GPRC5D present on MM cancer cells and CD3 receptors present on the T cells of the immune system.[1] Published literature has attributed this distinct GPRC5D target to longer term maintenance of immune function compared to BCMA-targeting treatments.[42, 43]

Survival benefits

- The clinical efficacy and safety of talquetamab in patients with TCE RRMM is demonstrated in MonumenTAL-1, a first-in-human, Phase I/II, ongoing single-arm trial.[44]
- A robust indirect treatment comparison (ITC) of talquetamab was conducted against the current SoC, teclistamab, based on individual patient data (IPD) from MonumenTAL-1 and MajesTEC-1, respectively (see Section 2.10). The findings of this trial-vs-trial ITC demonstrated that talquetamab provides significantly higher overall response rates (ORRs) than teclistamab, alongside similar rapid and deep responses observed with both talquetamab and teclistamab.
- Whilst talquetamab is associated with comparable progression-free survival (PFS) to teclistamab, talquetamab provides statistically significant and clinically meaningful improvements in OS compared to teclistamab. Talquetamab significantly reduces the risk of death by [redacted]% (see Section 2.10) compared to teclistamab, demonstrating that it represents an efficacious alternative treatment that will improve patient prognosis.

Improved infection-related safety profile

- When compared with BCMA-targeting TCR treatments which may impair the ability of the immune system to resolve infections.
- Talquetamab, a GPRC5D-targeting BsAb, has a lower Grade 3/4 infection rate than teclistamab ([redacted]% versus [redacted]% respectively).[45, 46] Talquetamab was also associated with a reduced rate of infection-related mortality compared to teclistamab ([redacted]% [redacted]/154 patients] versus [redacted]% [redacted]/165 patients] respectively; see Section 2.11.4).[45, 46] Only [redacted]% of the deaths ([redacted]/[redacted]) in MonumenTAL-1 were due to infection, compared to [redacted]% ([redacted]/[redacted]) in MajesTEC-1.
- Patients consulted as part of the NICE appraisals for BCMA-targeting BsAbs [TA1015 and TA1023] and patients consulted as part of the market research conducted by the Company expressed their fear of contracting infections and the detrimental impact on their daily lives, further emphasising the value of treatment options with an improved infection-related safety profile.[3, 8, 16]

Healthcare resource use benefits and improved convenience for patients

- Owing to the reduced infection rate, talquetamab is anticipated to have a reduced intravenous immunoglobulin (IVIg) use compared to BCMA-targeting BsAb therapies. IVIg is a strained resource in the UK which remains costly for the NHS to administer.[3] Consequently,

the reduction of IVIg with talquetamab ([redacted]% compared to [redacted]% with teclistamab) would also be associated with reduced healthcare resource use compared to teclistamab.[45, 46]
- Additionally, talquetamab will confer healthcare resource use benefits owing to its flexible dosing regimen; unlike teclistamab or elranatamab, patients can receive talquetamab biweekly from the outset of treatment.[16] Talquetamab would therefore also meet patients' needs for a treatment that does not require them to attend hospital so frequently.[16]

Preservation of QoL benefits

- Similar to teclistamab, talquetamab is a dexamethasone-free regimen, avoiding the need for concomitant steroid use and thereby, preserving the QoL benefits associated with teclistamab.
- Whilst talquetamab is associated with GPRC5D-specific AEs which are otherwise not associated with BCMA-targeting BsAb therapies, these AEs are generally well managed with low rates of talquetamab discontinuation or dose modification and [redacted] fatal outcomes.[46] In comparison, BCMA-targeted BsAb therapies are associated with an increased risk of severe infections (i.e., Grade 3/4 infections) and infection-related mortality, so talquetamab may reduce infection-related anxiety and result in further QoL benefits compared to BCMA-targeting BsAb treatments.[45, 46]

Conclusions

- If recommended, talquetamab will address the clear unmet needs for TCE RRMM patients and their clinicians by providing an additional efficacious treatment option with a reduced risk of severe infections and a more flexible dosing regimen.
- As presented in Section 3, a cost-utility model was developed to estimate the cost-effectiveness of talquetamab compared to teclistamab in TCE RRMM patients after at least three prior lines of therapy. The results of the economic analysis demonstrated that talquetamab has not only the potential to address the significant unmet need for an alternative efficacious treatment option but also represents a cost-effective use of the NHS resources.

1.3.1 Disease Overview

Presentation

MM is a rare and predominantly incurable haematological cancer characterised by the excessive proliferation of malignant plasma cells within the bone marrow. These cells produce an abnormal monoclonal Ig called M-protein, which accumulate in the bones, blood and multiple organs throughout the body.[47-49] Over time, this accumulation leads to progressive morbidity and eventual mortality by compromising the body's ability to fight infections and causing serious complications which require immediate medical treatment, including elevated calcium levels (hypercalcemia), renal impairment, anaemia and bone disease (CRAB).[47, 50]

Patients with MM experience numerous debilitating symptoms including fatigue, bone pain, recurrent or persistent infection and hyperviscosity, all of which significantly impact their HRQoL on a daily basis.[47, 50, 51]

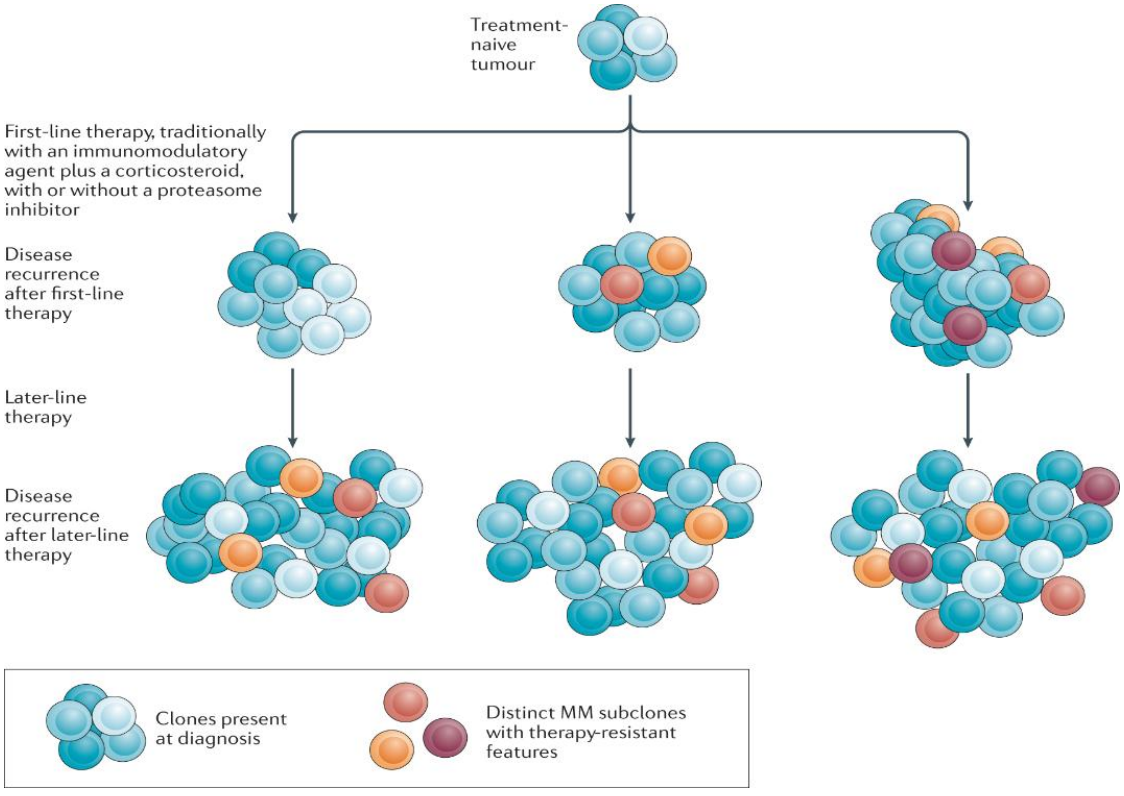
Heterogeneity

MM is a highly heterogeneous disease with a variable clinical course, and as such, prognosis varies greatly from patient to patient depending on a number of factors. At a genetic level, MM exhibits diversity due to mutations and genetic translocations.[52] Central to MM's evolution is the acquisition and accumulation of secondary genetic events, such as additional chromosomal

translocations, copy-number variations, epigenetic modifications, and single nucleotide somatic mutations.[53-55] These genetic changes contribute to MM progression and the development of drug resistance, as depicted in Figure 2.

Patients often experience remission periods followed by relapse, which then continues in cycles of relapse and remission with each line of therapy.[56] Unfortunately, each subsequent relapse carries a higher risk of additional clones arising due to genetic mutations within the myeloma cells.[57] Nearly all patients will experience disease relapse and become refractory to at least one class of drugs commonly used for MM treatment.[58] Understanding this genetic complexity is crucial for tailoring effective therapies with novel targets in order to improve outcomes for MM patients. The pace of innovation in MM has accelerated in recent years. Recently new MM therapies have been developed against novel targets such as signaling Lymphocytic Activation Molecule Family member 7 (SLAMF7), cluster of differentiation 38 (CD38), Fc receptor homolog 5 (FcRH5), programmed death ligand 1 (PDL1), programmed death receptor 1 (PD1), and cluster of differentiation 56 (CD56).[59-63] Improving upon established mechanisms of disease control also moves at pace with the development of Cereblon E3 ligase modulatory drugs (CELMoDs), targeted chemotherapy and next generation PIs.[64]

Figure 2: Genetic heterogeneity and clonal evolution cause drug resistance in MM



Abbreviations: MM: multiple myeloma.
Source: Mikkilineni and Kochenderfer (2021).[65]

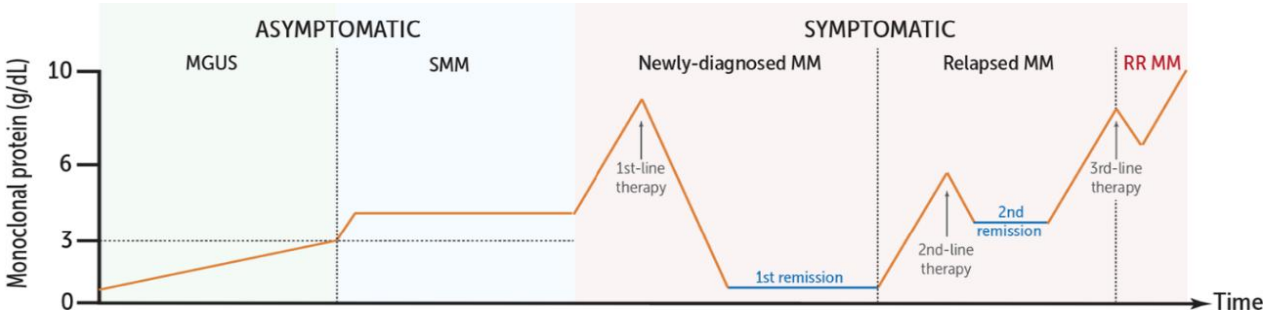
Treatment challenges

MM remains a predominantly incurable malignancy, and nearly all patients eventually experience relapse or fail to respond to treatment, becoming refractory to available options.[20]

The clinical journey of MM and progression to RRMM as outlined by the International Myeloma Working Group (IMWG) is illustrated in Figure 3.[66] MGUS (monoclonal gammopathy of

undetermined significance) and smouldering MM (SMM) are asymptomatic precursors to newly-diagnosed MM, at which point, patients experience symptoms of their disease. RRMM is characterised by non-responsiveness during salvage therapy or progression within 60 days of last therapy, even in patients who achieved minimal response (MR) or better previously.[67-69]

Figure 3: Clinical model of disease progression in MM



Abbreviations: MGUS: monoclonal gammopathy of undetermined significance MM: multiple myeloma; RRMM: relapsed/refractory multiple myeloma; SMM: smouldering multiple myeloma.
Source: Ho *et al.* (2020).[70]

Patients previously exposed to an IMiD, a PI, and an anti-CD38 mAb and who have progressed on their last therapy (i.e., patients with TCE RRMM) have limited treatment options. As noted in Section 1.1, BCMA-targeting TCR therapies are recommended by NICE for the treatment of TCE RRMM in the 4L+ setting.[2,3] Given the substantial clinical and economic benefits these therapies have demonstrated versus prior SoC in this setting, BCMA-targeting BsAb therapies, such as teclistamab, are anticipated to represent the new SoC in UK clinical practice in TCE RRMM patients.

The recent addition of teclistamab to the TCE RRMM treatment pathway represents a step-change in the management of patients with TCE RRMM, offering a novel and effective treatment option in patients who otherwise face treatment using therapies with poor efficacy.[3] Despite this, owing to the relapsing and incurable nature of RRMM, survival outcomes in this population remain limited; median OS in TCE RRMM patients is anticipated to be 22.2 months.[3]

Additionally, BCMA-targeting immunotherapies, have been associated with higher rates of all-Grade and ≥Grade 3 infections, relative to other non-BCMA-targeting MM therapies. This is due to off-target effects on patients' B cells and plasma cells, which can impede the ability of the humoral immune system to fight infection.[32-39] As discussed further in Section 1.3.3, these infections can be life threatening and cause anxiety for patients, and treating them has a substantial resource impact on the NHS as it requires the use of IVIg.

1.3.2 Epidemiology

In the UK as a whole, between 2017–2019, 6,240 MM cases were diagnosed annually, accounting for approximately 2% of all new cancer cases, as well as 2% of all cancer-related deaths.[71] Based on the incidence of MM in England being 0.01%, the budget impact model for this submission estimates an average of 4,563 patients with MM in England.[72]

Since the early 1990s, myeloma incidence rates have increased by more than a third (36%) in the UK.[71] Specifically, rates increased by 25% and 40% in females and males, respectively.[71]

Projections indicate that, on average, there will be approximately 8,300 new cases of myeloma annually in the UK by 2038–2040.[71]

Several factors are associated with an increased risk of developing MM:[18, 73-75]

- Age: MM most commonly affects individuals over the age of 60.[71]
- Race: Individuals with African heritage experience MM at twice the frequency of Caucasian people.[75]
- Family history: Family clusters of MM have been observed, though the underlying predisposing genetic mutations are unclear. Retrospective results from the Multiple Myeloma Consortium found that individuals with first-degree relatives with MM were almost twice as likely to be diagnosed with MM versus individuals without first-degree relatives with MM.[75]
- Exposure to radiation or chemicals: Individuals exposed to radiation or certain chemicals (such as asbestos, benzene and pesticides) face an elevated risk of developing MM.[73]
- Sex: MM is more prevalent in men, with suggested underlying factors including health-risk behaviours such as smoking, alcohol consumption and obesity.[75] In England, between 2017–2019, incidence rates were 62% higher in males versus females.[71]

As noted in Section 1.3.1, despite advances in treatment, at present, MM remains predominantly an incurable disease. Its clinical course varies significantly due to disease heterogeneity; some patients progress rapidly despite treatment, while others remain stable without therapy for years. Ultimately, all surviving patients will relapse and progress due to residual disease.[18]

Epidemiological data on patients with TCE RRMM is scarce. This limitation arises from the rare nature of the condition, affecting approximately 4.6 in 10,000 persons in the European Union.[9] The NICE resource impact template for TCE RRMM that was developed during the appraisal for teclistamab [TA1015] estimates that 15% of MM patients in England go on to become TCE, representing approximately 785 patients in current clinical practice.[3, 76] This value is expected to grow to 823 after 5 years.[76] Based on the latest available epidemiological data, the budget impact model designed for this submission indicates that around 684 patients would receive a diagnosis of TCE RRMM and commence 4L+ treatment annually.

1.3.3 Burden of TCE RRMM and impact on patients and carers

Symptom Burden

MM imposes a significant clinical burden on patients. MM disrupts the normal balance between osteoclast and osteoblast activity, leading to increased bone tissue resorption. Consequently, patients face multiple complications including osteopenia (an elevated risk of bone fractures) and the development of osteolytic bone disease caused by the accumulation of cancerous plasma cells.[77] Furthermore, more than two thirds of all MM patients experience anaemia due to disease-related complications.[78]

The results of a meta-analysis of 34 studies capturing 3,023 patients with MM identified fatigue, pain, constipation and tingling in the hands/feet as the most common disease-related symptoms.[79] Additionally, over half of all participants reported decreased physical, cognitive, emotional, and social functioning as a result of their disease.[79]

As MM progresses to RRMM, the disease burden intensifies. Patients with relapsed/progressive disease report more severe and numerous symptoms as well as treatment related complications compared to those with newly diagnosed or stable MM, including weakness, fatigue, bone pain, weight loss, confusion, excessive thirst and constipation.[80] Moreover, the results of a 2021 cross-sectional, multicentre study conducted in symptomatic RRMM patients (N=184) found disease- and treatment-related symptoms more significantly impacted RRMM patients overall life satisfaction versus patients without relapsed/refractory disease (p=0.0335) and resulted in significantly worse single-item quality of life (SIQOL) scores.[24] Additionally, the study demonstrated that patients with RRMM had higher Myeloma Patient Outcome Scale (MyPOS) scores than those with newly diagnosed or stable MM, underscoring the substantially increased disease burden faced by RRMM patients versus patients without relapsed/refractory disease.[24]

The symptom burden worsens with each line of therapy and therefore is particularly acute in TCE RRMM patients who have received at least three prior lines of therapy.[24, 25]

Impact on HRQoL

In addition to the physical symptoms of the disease, MM significantly impacts the mental and emotional wellbeing of patients, leading to substantial reductions in their quality of life.[26, 27] Of note, MM is associated with the lowest patient quality of life of all haematological cancers.[26, 27] A 2019 study by NICE focusing on patient preferences in MM revealed that 'Fatigue and tiredness' had the most detrimental impact on patients' (n=97) lives.[81] Additionally, MM affected their personal life by reducing their sense of control/independence, altering their lifestyles, and causing financial strain.[81]

A diagnosis of MM has a profound psychological impact, with patients experiencing fear due to the unpredictability of the disease. Some patients even describe their diagnosis as a ticking 'time bomb', living in constant fear of a relapse.[82] This is evident in worsening HRQoL scores at one year follow up, with over a third of patients worrying about their future health and one in five patients fearing dying.[22] Additionally, depression affects one in four MM patients.[83]

Patients consulted by Myeloma UK during the NICE appraisal for teclistamab [TA1015] commented on how their disease has impacted their QoL:[3]

"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."

"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo."

Above all, owing to the poor prognosis and the impact this has on patients emotional and psychological wellbeing, patients with RRMM experience worse HRQoL compared to patients with newly diagnosed/non-relapsed or refractory MM, as well as those with other cancer types.[21, 23, 84] Initial disease relapse is associated with a period of negative emotions, including hopelessness and resignation.[85] Subsequent relapses are linked to increasing distress and pessimism.[85] As a result, HRQoL significantly deteriorates with each relapse and subsequent line of treatment (LoT).

This was observed in the LocoMMotion study (a real-world prospective study that investigated treatment patterns and outcomes in RRMM patients who had undergone at least three prior therapies, across 86 sites in Europe and the United States [including the UK]) where TCE RRMM patients (n=99) reported worse global health status, physical functioning, and symptoms of pain and fatigue compared to baseline.[86] This evidence highlights the substantial HRQoL burden for TCE RRMM patients who have advanced and heavily treated disease. This burden becomes especially pronounced when patients have limited effective treatment options left, as is the case for TCE RRMM patients in UK clinical practice.[85, 87] Patients have expressed their concern about running out of options when they reach 4L+ and would find reassurance in knowing that additional efficacious options are available.[16] Indeed, this is in line with insights gathered from patients interviewed as part of a market research conducted by the Company for this submission.[16]

Patients consulted as part of the market research conducted by the Company expressed that BCMA-targeting BsAb therapies remain the only effective treatment options for TCE RRMM patients in the 4L+ setting:[16]

"When you get to the number of treatments that he has had, your options are reduced because you have to stick to a pathway. You might only have one option. Fortunately, the timing for him meant he could have this new treatment [teclistamab]. If he was in a position where they were saying, "this is the end of the line", he would feel really, very differently. In the early diagnosis days, we knew people who were unfortunately in that position where they didn't have another treatment option." **– *Caregiver of a TCE RRMM patient currently receiving teclistamab***

This HRQoL burden is further increased by the fact that all MM treatments traditionally used in the relapsed setting, apart from BCMA-targeting BsAb therapies, require concomitant treatment with the corticosteroid dexamethasone. Dexamethasone is associated with high levels of toxicity and therefore has a significant impact on the daily lives of patients; causing mood swings, aggression, mania, insomnia and fatigue, which can be difficult for patients and their families to live with.[41]

Patients consulted by Myeloma UK during the NICE appraisal for teclistamab expressed their preference for treatment options that do not require concomitant steroid use:[3]

"All the other drugs I have had come with steroids. They cause lack of sleep, weight gain, muscular aches and a puffy neck. They are the drugs I have struggled with the most. I have always had to get my dose reduced."

"I have had a lot of treatments. The worst thing I have ever had is steroids. You are up and down and up and down. You feel like you can beat the world then crash."

The above highlights the substantial detrimental impact RRMM, and particularly TCE RRMM has on patients' QoL, underlining the need for further efficacious treatments that can alleviate the symptom and HRQoL burden imposed by the disease.

Treatment choice

As outlined in Section 1.3.1, teclistamab represented a step-change in improving survival outcomes in TCE RRMM patients. Teclistamab is expected to provide patients with an additional 12.4 months of life on average compared to the previous SoC, with the potential for this to be

much longer in patients experiencing deep responses.[3] However, MM remains a predominantly incurable disease, for which the prognosis remains poor, and progression remains an inevitable part of the patient's journey. As per the August 2023 data cut of the MajesTEC-1 trial, median PFS and OS in patients receiving teclistamab were 11.4 months (95% confidence interval [CI]: [redacted]) and 22.2 months (95% CI: [redacted]), respectively.[40] Efficacious treatment options are therefore still needed for TCE RRMM patients, that will result in further improvements in prognosis, allowing patients to spend more time with their loved ones.[40] This is echoed by patients with RRMM, who feel that there is a need for more treatments, especially for those who are "young and active and can contribute generally to society", highlighting the preference for additional therapies that can extend their lives and improve their wellbeing.[3]

Similarly, patients consulted as part of the market research conducted by the Company expressed the desire for effective treatment options which prolong their life expectancy:

"I want my current treatment to last for a long time. Because most of the other treatments have relapsed in actually quite a short time, I mean when I had my stem cell transplant, a chap who sang in the choir with me, he had one at exactly the same time, and seven years on he's still in remission. Everything I've had hasn't lasted that long. So, one wish would be that the elranatamab would continue working and that I wouldn't relapse from it, and that goes into no more relapses. Perhaps a relapse every eight years or something, rather than after eight months." ***– TCE RRMM Patient, currently receiving elranatamab***

Teclistamab is currently the only effective treatment that is specifically licensed and routinely recommended for TCE RRMM patients in the NHS.[3] Therefore, an unmet need remains in this population for additional efficacious treatment options to facilitate both clinician and patient choice. Providing patients with choice and tailoring treatment to their individual needs is a fundamental aspect of NHS care and service and is extremely important in giving patients an increased sense of control over their disease.[30, 31]

In addition, patients consulted by Myeloma UK during the NICE appraisal of teclistamab indicated the importance of providing additional treatment choices, and felt that currently, once they progressed beyond 4L/5L, the options "*quickly diminish*", causing anxiety and impairing their QoL.[3] The importance of treatment choice in providing patients with a more positive perspective of their disease has also been emphasised by UK clinical experts, who highlighted the benefit of alternative treatments options with different targets and distinct mechanisms of action.[16]

Having to attend hospital for treatment can have a substantial burden on patients; it may be inconvenient for them and is associated with an emotional burden. For instance, patients receiving BCMA-targeting TCR therapies like teclistamab must begin on a weekly dosing regimen for at least the first six months of treatment before the consideration to transition to a biweekly dosing regimen if a complete response or better (≥CR) is achieved.[12, 88]

Patients consulted as part of the market research conducted by the Company commented on the need for treatments that require fewer visits to the hospitals:

"My current treatment is weekly dosing for six months, and then it feels a touch up in the air. I'm holding on to the idea that it goes down to fortnightly, I'm not sure where I've got this idea from, but I do have this idea that it goes down in six months' time. I know that it's not one that stops, so it isn't like [you have it for] six months and then that's it, you don't have any more treatment. It's six

months, and then either it continues to be weekly, or it goes down, I think it depends on the effect and where you're at, at the time." ***– TCE RRMM Patient, currently receiving elranatamab***

This highlights the unmet need for additional treatment options for patients that can be administered less frequently and more flexibly, allowing patients to feel a stronger sense of normalcy. This will in turn have benefits for the NHS in terms of healthcare resources given fewer staff and associated resource required.

Risk of infections

Patients with MM, and particularly those with RRMM have a high risk of infection.[33, 89-91] Clinical experts consulted by the Company also added that TCE RRMM patients with severe comorbidities, such as chronic obstructive pulmonary disease (COPD) and poorly controlled diabetes, have a significant risk of infection-related mortality and would therefore benefit in particular from treatments with a lower infection risk.

However, as outlined in Section 1.3.1, it is well-established in the literature that BCMA-targeting therapies are associated with higher rates of all-Grade and ≥Grade 3 infections, relative to other non-BCMA targeting MM therapies. This is due to off-target effects on patients' B cells and plasma cells, which can impede the ability of the humoral immune system to fight infection.[32-39, 42, 92-94] As such, there may be a preference by clinicians and patients to use a non-BCMA-targeting therapy in some instances, where clinically appropriate.

Many patients will require treatment with IVIg to mitigate the infection-related morbidities associated with BCMA-targeting T cell therapies and as outlined in the recent appraisal of teclistamab [TA1015], the demand for immunoglobulin is constrained by tight supply in UK clinical practice.[3] Insights from market research conducted by the Company indicated that this concern pertaining to the risk of infection persists among patients and clinicians in 2025.[16] Treatment with IVIg can be inconvenient for patients, as it may disrupt their treatment and is also costly for the NHS. Consequently, providing IVIg for TCE RRMM patients with infections imposes a considerable resource intensity burden on both patients and the NHS.[71,95]

The increased risk of severe infection and infection-related mortality has a highly detrimental impact on patients' QoL as they constantly fear contracting infections. Patients with TCE RRMM who were consulted by Myeloma UK during the NICE appraisal for BCMA-targeting BsAbs commented on the impact that infections have on their daily lives, their treatment, and on healthcare resources:[3, 96]

"The main side effect I've experienced is infections. I get so many viruses, constant colds, sometimes more than one. My treatment has been stop, start, stop, start. One of the downsides of having to start and stop is the need to be monitored for cytokine release syndrome [CRS] when restarting treatment. It means I have been in hospital a lot in the last year."

Patients who are currently receiving BCMA-targeting BsAbs who were consulted as part of the market research conducted by the Company have similarly expressed such concerns and fear of contracting infections:[16]

"We have a constant, not battle, but conversation about work and whether I can keep working. I used to do a lot of international travel as well for work, and to some extent we've tried to accommodate some of that. Also, I'm in a lecture theatre or I'm teaching, I've got groups of

students who are probably coughing up their lungs and whatever else. My consultant did say that my current treatment will make me really immunocompromised, you might want to think about work again. That was part of the reason also that we started it in December, so before Christmas, because then I could get through some of the treatment initiation before I started teaching. I haven't stopped working, and I haven't stopped teaching, but the measures that we've put in place are that I teach first thing in the morning before everyone has coughed in the room. Then with the hope that I won't pick anything up really." – ***TCE RRMM Patient, currently receiving elranatamab***

An unmet need therefore exists for additional TCE RRMM treatments with alternative targets and/or mechanisms of action, that are associated with a lower risk of severe infections and can therefore reduce the impact infections have on both the QoL of the patient and on NHS resources.

Effect on Carers

Beyond the direct impact of the disease on patients, MM also has a detrimental impact on their carers. Most of the clinical management of MM is provided in the outpatient setting. As such, the bulk of care is delivered informally by family members or friends. A recent study sponsored by the Company surveyed 120 carers of patients with MM to assess the impact caring has on their QoL.[97] In total, [redacted]% of the carers were the partner or spouse of the patient, and [redacted]% were the child of a MM patient.[97] In this study, [redacted]% of caregivers surveyed felt that caregiving had affected their work life, with [redacted]% of caregivers reporting that they had to frequently take time off.[97]

The informal carers of MM patients are anticipated to be associated with a particularly poor QoL compared to carers in other disease areas where care is delivered formally by professional carers. This is owing to informal carers having a strong emotional attachment to the patient and therefore likely experiencing increased fear and anxiety versus formal carers over potentially losing their loved one.[83] In the aforementioned study sponsored by the Company, [redacted]% of carers reported moderate anxiety/depression, and [redacted]% of the carers reported severe or extreme anxiety/depression.[97]

The emotional toll of MM and the impact on HRQoL are significant, and patients require comprehensive support. The carers of patients with MM experience a high burden related to providing direct care (e.g., monitoring, administering medications, scheduling appointments, performing technical procedures, communicating with healthcare providers), coordinating care (e.g., transportation, communication, household maintenance), and providing emotional support to patients.[28, 29] Furthermore, a targeted literature review carried out by the Company in 2023 to capture the quantitative impact of caregiving on the HRQoL of carers of patients with MM, reported that MM carers often experience reduced HRQoL due to increased stress levels, reduced productivity and financial strain.[98]

Caregivers of patients with TCE RRMM who were consulted as part of the market research conducted by the Company shared the strains caring for a MM patient poses to them:[16]

"Most of the time I'm absolutely fine and I deal with it, but I will be the one that has to step in to report anything for him. If there's anything that needs dealing with, he knows I'll do it. I'd rather get involved than sit and worry about it." ***– Caregiver of a TCE RRMM patient currently receiving teclistamab***

"I used to carry all of his notes around with me because whoever was there just didn't know what to do." **– *Caregiver of a TCE RRMM patient currently receiving teclistamab***

The introduction of a treatment option with an alternative and flexible dosing schedules which minimises number of hospital visits may therefore impact carers by alleviating the burden of such trips required.

Summary

In summary, TCE RRMM poses a significant burden on patients, in terms of both the symptom burden and the associated detrimental impact on HRQoL. This burden extends beyond patients to their caregivers, who are predominantly comprised of the patients' own family and friends. Although outcomes in TCE RRMM patients are improving, teclistamab remains the only effective treatment that is routinely commissioned in TCE RRMM patients, and further improvements in prognosis are needed. An unmet need therefore exists for efficacious, treatment options with alternative targets, a reduced risk of severe infections and a more flexible dosing regimen, that will improve survival for patients, without compromising their QoL.

1.3.4 Clinical management of TCE RRMM and positioning of talquetamab in the treatment pathway

Treatment Guidelines

A variety of European, US and worldwide guidelines are available in the MM disease area, including: the European Haematology Association (EHA) and the European Society for Medical Oncology (ESMO) (published in 2021),[99] the Internation Myeloma Working Group (IMWG) (published in 2021),[100] and the National Comprehensive Cancer Network (NCCN) (published in 2023).[101] Specific to the UK, the British Society for Haematology (BSH) has published guidance (2021) on the diagnosis and initial treatment of MM, but this does not provide specific recommendations for TCE RRMM.[102] The guidelines considered most relevant to the management of MM in the NHS, and therefore informing the treatment pathway below, are NICE's guidelines for the treatment of RRMM (NG35, published in 2016).[103]

Current UK Clinical Pathway

A summary of the treatments recommended by NICE for routine commissioning in patients with MM are outlined in Figure 4, which is additionally supplemented by NICE recommendations for CDF funding and UK clinical expert advice.[3, 104-107]

In UK clinical practice, patients with newly diagnosed MM are initially assessed for suitability for autologous stem cell transplantation; patients eligible for stem cell transplantation are typically treated with daratumumab (an anti-CD38 mAb) in combination with bortezomib (a PI), thalidomide (an IMiD), or dexamethasone (a glucocorticoid).[103, 108] Patients who are ineligible for autologous stem cell transplantation typically receive treatment with daratumumab in combination with lenalidomide (an IMiD) and dexamethasone.[103]

Regardless of prior autologous stem cell transplant history, in patients whose disease progresses such that they become relapsed/refractory, treatment is highly individualised and dependent on

response to previous treatment. Patients receive treatment with the following three classes of treatment in a varying order and in varying combinations:[103]

- PIs (e.g., bortezomib, carfilzomib or ixazomib),
- IMiDs (e.g., lenalidomide, thalidomide or pomalidomide),
- Anti-CD38 mAbs (e.g., daratumumab or isatuximab)

Due to the disease pathophysiology, patients do not typically receive treatments with the same drug target as a previous treatment until all other treatment classes are exhausted. This is due to recycling of existing therapies in RRMM having limited efficacy, as patients are re-exposed to treatments or classes of agents that they have previously developed resistance to. Once a patient has received at least one of each of these three treatment classes, they are defined as triple-class exposed (TCE).

NICE's recommendation for teclistamab also introduced the novel BCMA-targeting mechanism of action for the treatment of TCE RRMM to the routinely commissioned UK treatment pathway. BCMA is typically overexpressed on myeloma cells so by also engaging T-cells, teclistamab can direct the immune system to specifically target the cancerous cells.[2]

In addition to the treatment classes above, therapies with alternative mechanisms of action such as selinexor have been recently approved for use for both the second line (2L; selinexor plus bortezomib plus dexamethasone) and fifth line (5L; selinexor plus dexamethasone) treatment of RRMM. Selinexor selectively inhibits nuclear export of tumour suppression proteins, inducing cell death in cancer cells.[6, 109]

TCE RRMM Clinical Pathway

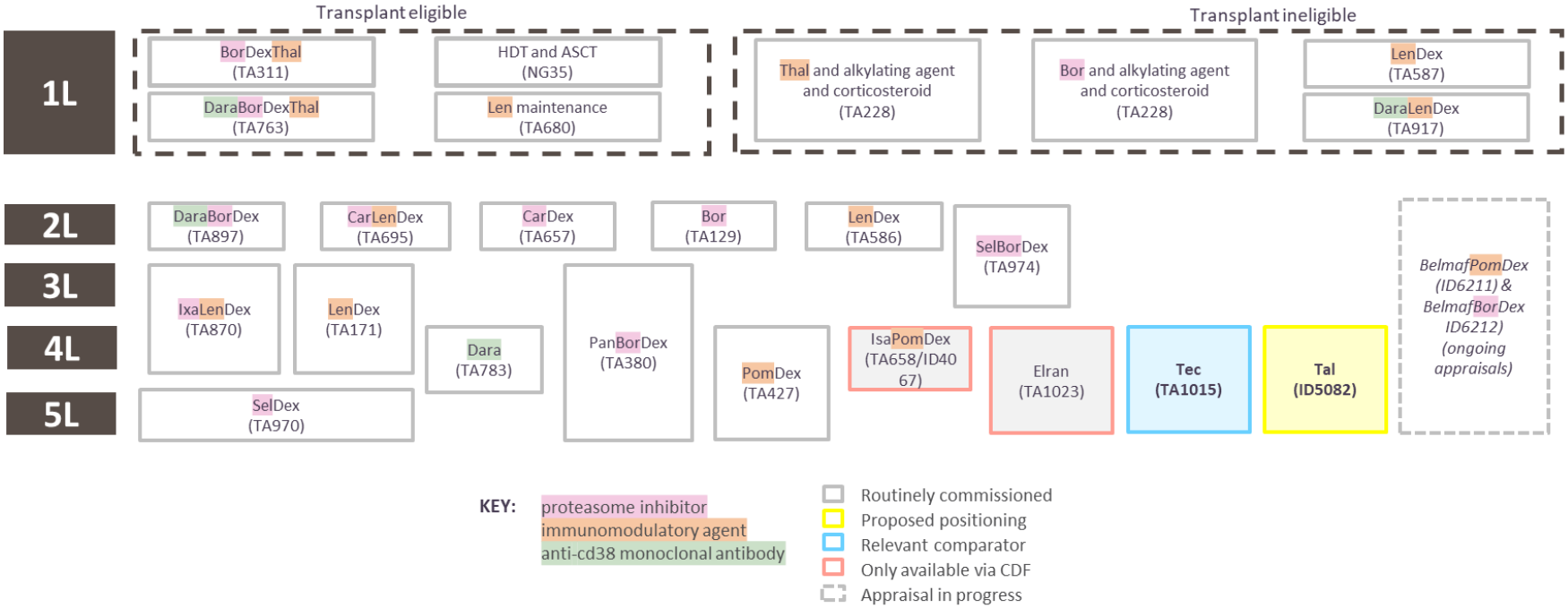
The current treatment options recommended by NICE for patients with RRMM who have received at least three prior lines of therapy are outlined in Table 3 below. In UK clinical practice, most treatments recommended in this setting are either used earlier in the treatment pathway (e.g., ixazomib plus lenalidomide plus dexamethasone [IxaLenDex]), or are either reimbursed via the CDF (e.g., elranatamab and isatuximab plus pomalidomide and dexamethasone [IsaPomDex]). Other treatments are currently undergoing appraisal (e.g., belantamab mafodotin plus pomalidomide and dexamethasone [BelPomDex] and belantamab mafodotin plus bortezomib and dexamethasone [BelBorDex]). As such, the comparators listed in Table 3 as not relevant do not represent routine clinical practice in TCE RRMM patients and are not relevant comparators to talquetamab in this submission.

Of the treatments outlined in Table 3, teclistamab is the only therapy specifically licensed and routinely recommended for patients with TCE RRMM in England and Wales.[3] Owing to its improved clinical- and cost-effectiveness over the previous SoC (PomDex, PanBorDex and SelDex), teclistamab is considered to be a SoC 4L+ treatment in TCE RRMM, as validated by feedback received by UK clinical experts.[3, 16]

With the recent recommendations of teclistamab and elranatamab (via the CDF), the population of TCR-exposed patients in the UK clinical practice is currently very small, consistent with the orphan designation of talquetamab in this setting.[3, 7, 8] As detailed in Section 1.1, given the rarity of the condition and the limited evidence base available, this submission is taking a pragmatic approach in which subgroup analyses in the TCE RRMM patient population (including the TCR-exposed population) will not be explicitly considered, and teclistamab is considered the most

relevant comparator to talquetamab for the purposes of decision making. This is demonstrated below in Figure 4.

Figure 4: The current NHS MM treatment pathway and proposed positioning of talquetamab



Abbreviations: 1/2/3/4L/5L: 1st/2nd/3rd/4th/5th line; ASCT: autologous stem cell transplantation; Belmaf: belantamab mafodotin; Bor: bortezomib; BsAb: bispecific antibody; Car: carfilzomib; CD38: cluster of differentiation 38; Dara: daratumumab; Dex: dexamethasone; Elran: elranatamab; HDT: high dose therapy; Isa: isatuximab; Ixa: ixazomib; Len: lenalidomide; MM: Multiple Myeloma; NHS: National Health Service; Pan: panobinostat: Pom: pomalidomide; PomDex: pomalidomide plus low dose dexamethasone; RRMM: relapsed/refractory multiple myeloma; Sel: Selinexor; TA: technical appraisal; TAL: talquetamab; TCE: triple-class exposed; TCR: T-cell redirecting; Tec: teclistamab; Thal: thalidomide.
Source: NICE Myeloma Diagnosis and Management.[103] NICE. Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1023].[8] NICE. Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1015].[3] NICE. Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211].[106] NICE. Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212].[107]

Table 3: Summary of treatments for patients with RRMM who have received three prior therapies, listed as part of the NICE final scope and justification for relevance

Treatment	Relevant	Justification
Relevant comparator		
Teclistamab	Yes	Evidence provided in the recent NICE appraisal of teclistamab [TA1015] demonstrated that teclistamab is associated with significant clinical- and cost-effectiveness benefits over previous SoC (PomDex, PanBorDex and SelDex) in 4L+ TCE RRMM.[3] Teclistamab is anticipated to be used preferentially over these treatments in TCE RRMM in the 4L+ setting in UK clinical practice, as supported by UK clinical experts, and therefore teclistamab represents the most relevant comparator for the purposes of decision making.
Excluded comparators		
Pomalidomide plus low-dose dexamethasone (PomDex)	No	The Company acknowledges that in the UK there is likely to be an emerging group TCR-exposed TCE RRMM patients.[3-6] However, due to the recency of the recommendations for both teclistamab (Q4 2024) and elranatamab (Q4 2024, via the CDF), the population of TCR-exposed patients in UK clinical practice is currently very small, which is consistent with the orphan designation status of talquetamab in this indication.[7] Given that the evidence base in 5L+ TCR exposed patients remains limited due to the rarity of the condition;[9] and that teclistamab recently demonstrated clinical and cost-effectiveness benefits against the previous SoC treatment options available to TCR-exposed patients, this submission therefore takes a pragmatic approach in which the demonstration of clinical- and cost-effectiveness of talquetamab versus teclistamab will, by extension, demonstrate clinical- and cost-effectiveness of talquetamab versus PomDex, PanBorDex and SelDex. These treatments are therefore not the most relevant comparators to talquetamab in this setting in this submission.
Panobinostat plus bortezomib and dexamethasone (PanBorDex)	No	
Selinexor plus dexamethasone (SelDex)	No	
Isatuximab plus pomalidomide and dexamethasone (IsaPomDex)	No	Patients who are eligible for IsaPomDex represent a different cohort of patients to those eligible for talquetamab. Real-world evidence in the UK confirmed that over 95% of IsaPomDex patients are anti-CD38 mAb naïve and therefore are not classed as TCE, and would not be eligible to receive talquetamab.[11,110]
Belantamab mafodotin with pomalidomide and dexamethasone (BelPomDex; subject to NICE evaluation)	No	BelPomDex is currently undergoing appraisal by NICE in RRMM patients after 1 or more treatments.[106] As such, BelPomDex does not represent routine care and therefore is not a relevant comparator in TCE RRMM patients in UK clinical practice. Furthermore, as BelPomDex is undergoing appraisal by NICE in the 2L+ positioning, it is anticipated that it would be used earlier in the treatment pathway than the 4L+ setting. BelPomDex would therefore not represent a relevant comparator in TCE RRMM patients in UK clinical practice even if it is recommended.

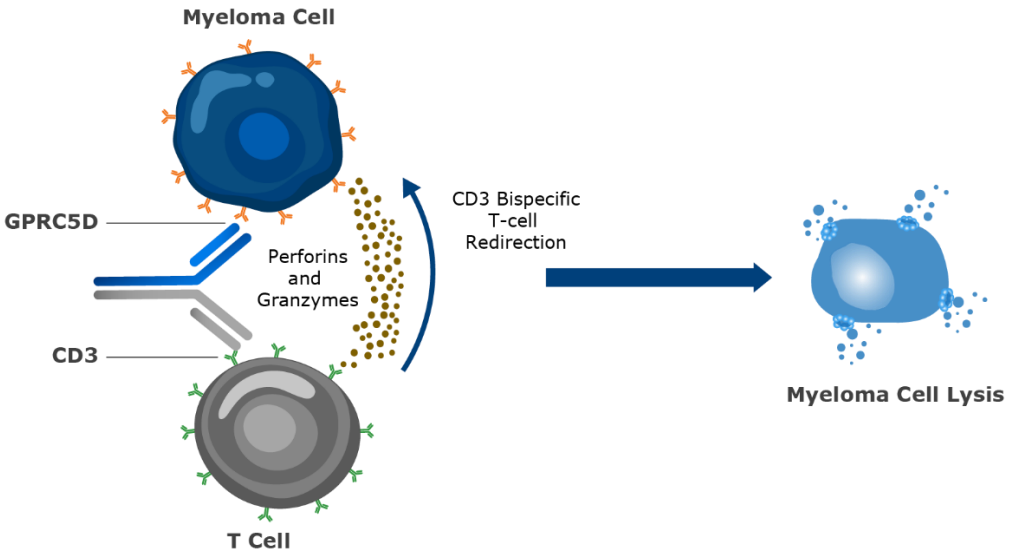
Belantamab mafodotin with bortezomib and dexamethasone (BelBorDex; subject to NICE evaluation)	No	As with BelPomDex, BelBorDex is currently undergoing appraisal by NICE in RRMM patients after 1 or more treatments. As BelBorDex is undergoing appraisal by NICE in the 2L+ positioning, it is anticipated that it would be used earlier in the treatment pathway than the 4L+ setting and therefore does not represent a relevant comparator in TCE RRMM patients, nor would it if it was recommended.[107]

Abbreviations: 1L: first line; 2L: second line; 3L: third line; 4L: fourth line; 5L+: fifth line and beyond; AEs: adverse events; BelMaf: belantamab mafodotin; BelPomDex: belantamab mafodotin with pomalidomide and dexamethasone; BelBorDex: belantamab mafodotin with bortezomib and dexamethasone; CDF: Cancer Drugs Fund; HRQoL: health-related quality of life; IsaPomDex: isatuximab with pomalidomide and dexamethasone; MM: multiple myeloma; NICE: National Institute for Health and Care Excellence; PomDex: pomalidomide plus low-dose dexamethasone; PanBorDex: panobinostat plus bortezomib and dexamethasone; RRMM: relapsed or refractory multiple myeloma; RWE: real-world evidence; SCT: stem cell transplant; SelDex: selinexor plus dexamethasone; SoC: standard of care; TCE: triple-class exposed; TCR: T-cell redirection; UK: United Kingdom.

Positioning of Talquetamab Within the Future UK MM Pathway

Talquetamab is a first-in-class, humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) TCR BsAb that binds to GPRC5D, present on MM cancer cells and CD3 receptors present on the T cells of the immune system. Talquetamab promotes enhanced T cell-mediated cytotoxicity through the recruitment of CD3-expressing T cells to GPRC5D-expressing cells.[1] This leads to the activation of T cells and induces subsequent lysis of GPRC5D-expressing cells mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells.[111] Talquetamab is able to preferentially target MM cells, which express the GPRC5D receptor, with minimal expression detected on B cells or B cell precursors.[1] With this mechanism of action, the recommendation of talquetamab would introduce a novel target of MM treatment into UK clinical practice.

Figure 5: The mechanism of action of talquetamab



Abbreviations: GPRC5D; G protein couple receptor class 5D; CD3: cluster of differentiation 3.
Source: J&J IM. TALVEY Medical Information. (2024).[13]

Talquetamab is licensed as a 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 or after the last therapy.[1]

It is anticipated that if recommended, talquetamab would be positioned for use in TCE RRMM patients alongside teclistamab. Feedback from UK clinical experts indicated that teclistamab currently represents a SoC for these patients and is therefore the most relevant comparator to talquetamab in TCE RRMM patients for the purposes of decision making. Further justification for the exclusion of comparators to talquetamab in TCE RRMM patients is provided in Table 3.

The introduction of talquetamab into the UK RRMM clinical pathway would meet the unmet needs outlined in Section 1.3.3. As detailed in Section 2.10, in an indirect treatment comparison (ITC), talquetamab provides meaningful improvements in OS compared to teclistamab, reducing the risk of death by [redacted]% (hazard ratio [HR]: [redacted] [95% confidence interval [CI]: [redacted], p[redacted]). This clearly demonstrates that talquetamab represents an efficacious treatment option for TCE RRMM patients, that will result in improvements in survival for TCE RRMM patients compared to teclistamab. As discussed further in Section 2.10.8, this [redacted]

[redacted]

With its' distinct GPRC5D target, that allows for longer term maintenance of immune function compared to BCMA-targeting treatments, talquetamab has a lower Grade 3/4 infection rate than BCMA-targeting BsAbs (as presented in Section 2.11.4).[46] A naïve comparison of infection rates in patients receiving the BCMA-targeting BsAb teclistamab with that of talquetamab showed that the BCMA-targeting BsAb was associated with[redacted] times more Grade 3/4 infections ([redacted]% versus [redacted]% respectively).[45, 46] This lower rate of severe infections may, amongst other reasons, [redacted] A naïve comparison demonstrated a reduced rate of infection-related mortality in patients receiving talquetamab compared to teclistamab ([redacted]% [redacted]/154 patients] compared with [redacted]% [redacted]/165] for patients receiving talquetamab and teclistamab, respectively).[45, 46] As a result, talquetamab is likely to be associated with a reduced IVIg use (and hence healthcare resource) compared to BCMA-targeting drugs ([redacted]% compared to [redacted]% with teclistamab).[45, 46] Crucially, patients receiving talquetamab will also have reduced emotional burden and anxiety surrounding infections.

Additionally, talquetamab may also have healthcare resource benefits over current BCMA-targeting BsAb treatments owing to its flexible dosing regimen. As outlined in Section 1.2, patients can receive talquetamab biweekly from the outset of treatment. This is very important for patients, who place high value on treatments that do not require them to attend hospital so frequently.[16] Talquetamab also allows for a reduction from biweekly to four weekly dosing for patients not responding to supportive care for weight loss and oral toxicity.[1] Nevertheless, few dose reductions were observed in patients receiving talquetamab in MonumenTAL-1 due to these adverse events.[46]

Like teclistamab, talquetamab is also a dexamethasone-free regimen. As outlined in Section 1.3.3, dexamethasone has a significant impact on the daily lives of patients.[41] As a monotherapy, talquetamab can provide patients with an additional dexamethasone-free treatment option in addition to teclistamab, thereby avoiding the burden that treatment regimens including dexamethasone have on patients, and not compromising on the improvements in QoL that teclistamab provides.

In summary, if recommended, talquetamab will address the significant unmet needs for TCE RRMM patients by providing patients and their clinicians the treatment choice they currently aspire for. Talquetamab represents an additional efficacious treatment option with a reduced risk of severe infections owing to its GPRC5D targeting mechanism of action. With a flexible and potential for patients to begin treatment on a biweekly dosing regimen, patients receiving talquetamab would be able to spend less time visiting the hospital, and more time with their loved ones.

Ongoing Studies and Future Management of RRMM

The landscape of MM is rapidly evolving, with ongoing changes in therapeutic approaches, including the potential introduction of therapies earlier in the treatment pathway in the UK. Specifically, more BCMA-targeting therapies are currently undergoing or are planned to undergo the NICE appraisal process from 2L onwards (e.g., antibody-drug conjugates, BsAbs, chimeric antigen receptor-T cell [CAR-T] therapies, etc).[106, 107, 112-114] As patients are less likely to be re-treated with a drug that has the same target at later lines of therapy due to increased resistance (as outlined in Section 1.3.1), there will be an increasing unmet need for treatments such as

talquetamab, that have a distinct target to BCMA, to sustain survival benefits and build on the improvements in prognosis in TCE RRMM patients. Talquetamab, with its distinct GPRC5D target, is already authorised for use across Europe, Canada and the USA.[7, 115, 116] The inclusion of talquetamab in the UK treatment pathway is therefore crucial for continuing to improve the health outcomes of MM patients that has been observed over the last decade.

1.4 Equality considerations

There are not expected to be any equality issues related to the use of talquetamab in the UK, if recommended in the full licenced population.

2 Clinical effectiveness

MonumenTAL-1, the pivotal trial for talquetamab, provides robust evidence for the clinical efficacy and safety of talquetamab for patients with TCE RRMM that is generalisable to UK clinical practice

- MonumenTAL-1 comprises three distinct cohorts.[46] Of these, UK clinical experts confirmed that Cohort C (N=154) is most relevant to UK clinical practice and therefore informs the primary evidence base for talquetamab in this submission. Cohort C included patients who were treated biweekly (Q2W) with a subcutaneous talquetamab dose of 0.8 mg/kg, which reflects the anticipated usage of talquetamab in the UK.
    - Cohort A included patients receiving a weekly dosing regimen of talquetamab (QW; 0.4 mg/kg), which is more resource intensive than the Q2W regimen in Cohort C, and less likely to be used in UK clinical practice. Clinical experts consulted by the Company estimated that 90% of patients would receive the Q2W regimen and 10% the QW regimen.
    - The majority (73.1%) of patients in Cohort B were previously treated with CAR-T therapies, which are not available in the UK, and therefore this population presents greater limitations for decision-making compared to Cohort A and/or Cohort C.[117]

Talquetamab provides a high ORR among patients with TCE RRMM, with rapid-onset and deep responses for most patients responding to treatment

- The primary endpoint used in MonumenTAL-1 was ORR, defined as the proportion of patients who achieved PR or better according to the IMWG criteria,[118] as assessed by independent review committee (IRC).
- At a median follow-up of 31.2 months, over two thirds of patients responded to treatment with talquetamab, with an ORR of 69.5%.[119]
- Talquetamab induced deep responses in those who achieved a response, with complete response (CR) reported in 40.3% of patients.[46]
- Responses to talquetamab were also rapid, with a median time to first response for patients in Cohort C of just [redacted] months (range, [redacted]) and a median DoR of 17.5 months (95% CI, 12.5, 25.1).[119]

These responses translated to sustained periods of remission and overall survival for patients who received talquetamab

- In Cohort C, the median PFS was 11.2 months (95% CI, 7.7, 14.6) and median OS was not reached (95% CI, NE, NE) after a median follow-up of 31.2 months.[119]
- The high 36-month OS rate of 60.8% (95% CI, 51.5, 68.8) indicates that the majority of patients are still alive after three years of talquetamab treatment, clearly demonstrating the sustained survival offered by talquetamab to TCE RRMM patients.[119]

A robust ITC using IPD from both MonumenTAL-1 and MajesTEC-1 demonstrated that talquetamab elicits statistically significant and clinically meaningful improvements in OS versus teclistamab, with a [redacted]% reduction in the risk of death over time

- In the absence of head-to-head evidence of talquetamab and teclistamab, an indirect treatment comparison (ITC) was required. In the ITC, the MajesTEC-1 cohort was reweighted to align with MonumenTAL-1 via an IPTW ITC using ATT weighting in line with NICE TSD17.[120] The ITC adjusted for all 17 key prognostic variables identified by clinical experts, and the two cohorts were well-matched following adjustment, with a standardised mean difference of <±0.2 for all variables.
- Compared to teclistamab, patients receiving talquetamab had a significantly higher likelihood of experiencing an overall response (relative risk [RR]: [redacted] [95% CI: [redacted]]; p=[redacted]), while having a similar likelihood of achieving a CR (RR: [redacted] [95% CI: [redacted],

p=[redacted]) and comparable DoR (HR: [redacted] [95% CI: [redacted]], p=[redacted]). Consistent with CR and DoR, talquetamab and teclistamab provide comparable PFS to TCE RRMM patients (HR: [redacted] [95% CI, [redacted], p=[redacted]).

- The trial-vs-trial ITC demonstrated that a statistically significant and clinically meaningful improvement in OS was observed for patients treated with talquetamab versus teclistamab, with a [redacted] reduction in the risk of death over time following average treatment effect in the treated (ATT) weighting, and a two-stage subsequent treatment adjustment to remove the effects of subsequent treatments not routinely available in UK clinical practice (HR: [redacted] [95% CI: [redacted]], p[redacted]).
- The results were consistent across an extensive range of additional sensitivity analyses including alternative weighting approaches, multivariate regression and propensity score matching, as well as analyses using the weighted combined Cohort A+C for talquetamab or varying the distribution of subsequent treatments (see Section 2.10.6) demonstrating the robustness of the results.

Talquetamab is well-tolerated, with a predictable safety profile similar to that of other BsAbs and is associated with manageable GPRC5D-specific AEs.

- At least one treatment emergent adverse event (TEAE) was experienced by [redacted] of patients in Cohort C of the MonumenTAL-1 trial, with [redacted] of patients experiencing at least one TEAE that was judged as being related to talquetamab.[46] However, only [redacted] patients ([redacted]%) discontinued talquetamab due to a TEAE, suggesting that AEs were generally manageable[46]
  - The most common TEAEs of any grade were CRS and dysgeusia, occurring in 75.3% and [redacted]% of patients, respectively. However, only 1 case of CRS and no cases of dysgeusia were ≥Grade 3, demonstrating that these AEs were generally low in severity and therefore, manageable in clinical practice.[119]
  - When compared with MajesTEC-1, the proportion of patients experiencing BsAb-specific AEs such as CRS and ICANS was similar for both talquetamab (CRS [any grade]: 75.3% and ICANS [any grade]: [redacted]%) and teclistamab (CRS [any grade]: [redacted]% and ICANS [any grade]: [redacted]%), highlighting the predictable safety profile of talquetamab. Given the introduction of BsAbs in UK clinical practice for MM treatment (i.e., via routine availability of teclistamab) and management of CRS and ICANS events associated with other disease treatments, clinicians would be familiar with management strategies and adequate measures can be put in place to manage such AEs.[46, 119]
  - Whilst GPRC5D is a novel target in the MM treatment landscape, GPRC5D-related AEs (i.e., dysgeusia, weight loss, skin disorders, rash and nail disorders) associated with talquetamab were manageable. The rates of dose discontinuation and reduction due to these AESIs were low with [redacted] fatal outcomes, indicating that they can be effectively managed with appropriate supportive care.[46]

As a GPRC5D-targeting treatment, talquetamab is associated with an improved infection-related safety profile compared to BCMA-targeting therapies, demonstrated via reduced rates of severe infections and infection-related mortality.

- It has been well-established that BCMA-targeting therapies, have been associated with higher rates of any Grade and ≥Grade 3 infections relative to other MM therapies.[32-36, 38, 39] Indeed, talquetamab was associated with approximately half the incidence of Grade 3/4 infections compared to teclistamab ([redacted]% versus [redacted]% respectively).[45, 46]
- Compared to teclistamab, talquetamab is associated with substantially lower infection-related mortality of [redacted]% ([redacted]/154 patients) compared to [redacted]% ([redacted]/165 patients) in MajesTEC-1.[45, 46] Additionally, infection-related mortality represented [redacted]% of all deaths in MonumenTAL-1, but [redacted]% of all deaths in MajesTEC-1. The reduction in severe infections and infection-related deaths with talquetamab [redacted]

- The risk of severe infections can be further mitigated with the administration of IVIg, which places considerable burden on both NHS resources and is inconvenient for patients to receive. The reduction in Grade 3/4 infections associated with talquetamab also translate to reduced IVIg use. Only [redacted]% of patients received IVIg for any reason in MonumenTAL-1, compared to [redacted]% in MajesTEC-1.[32-36, 38, 39]

Conclusions

- BCMA-targeting BsAbs like teclistamab currently represent the new SoC for TCE RRMM in UK clinical practice. However, the prognosis for these patients remains poor, and as such, efficacious treatment options that extend patients' survival are still needed.
- Talquetamab provides a significant and clinically meaningful improvement in survival for patients with TCE RRMM, reducing the risk of death by [redacted]% when compared to teclistamab, therefore representing the alternative efficacious treatment option that patients and clinicians aspire for.
- The consistency of the ITC results across the extensive scenario analyses demonstrated that the survival benefit is not driven by differences in the subsequent treatment distributions of patients in MonumenTAL-1 and MajesTEC-1.
- While multi-faceted, [redacted].
    - BCMA-targeting therapies have off-target effects on patients' normal B cells and their precursors. This is known to result in disruptions to patients' humoral immunity and impairments to their immune system function.[32-36, 38, 39]
    - Meanwhile, talquetamab [redacted].[43]
    - Consequently, as detailed in Section 2.11.4 and Section 2.11.5, patients receiving talquetamab have a substantially lower rate of serious infections and infection-related deaths than those receiving teclistamab. This data is supported by available real-world data on the risk of infection with anti-BCMA therapy.[121, 122] [redacted]
- The reduction in the rate of severe infections with talquetamab also results in a reduction in the requirement for IVIg as compared to BCMA-targeting BsAb therapies, thus partially relieving the healthcare resource burden that infection management has on the NHS, as well as the infection-related anxiety patients with TCE RRMM patients experience.
- The AEs that occurred commonly with talquetamab (i.e., CRS, ICANS) are well known to occur with other BsAb treatments for RRMM, meaning that clinicians would be familiar with the management strategies of such AEs and adequate measures can be put in place in treatment centres. The GPRC5D-related AEs were easily manageable, causing few patients to discontinue talquetamab and resulted in [redacted] fatal outcomes.
- As highlighted in Section 1.3, similar to teclistamab, talquetamab is a dexamethasone-free treatment regimen, allowing patients to avoid the negative impact associated with corticosteroid use, which is often concomitantly used with other MM treatment regimens in the fourth-line setting and beyond.[3]
- Talquetamab, therefore, addresses the unmet need for effective, tolerable and dexamethasone-free treatment options for patients with TCE RRMM, that have an improved infection-related safety profile compared to BCMA-targeting BsAbs; thus providing patients and clinicians with the treatment choice that they currently desire.

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence for the efficacy and safety of treatments for patients with TCE RRMM. The original clinical SLR search was conducted on 26th May 2020 and updated on 22nd January 2021. All searches were subsequently updated in April 2022, May 2022, February 2023 and October 2023, with the most recent update conducted in December 2024.

Following removal of duplicates, a total of 946 records across all searches were screened at the title and abstract stage, of which 135 records were reviewed at the full-text stage. After exclusion of records not meeting the eligibility criteria, 87 records (reporting on 27 unique studies) reporting on either talquetamab or teclistamab were included in the SLR.

Of those, only two studies, MonumenTAL-1 and MajesTEC-1, were selected as relevant evidence for the submission. These were two out of four identified interventional studies, with the other two studies being small in sample size (OPTec, NCT05972135, N=6 participants) or focused on a Japanese population, also with a much smaller sample size compared with MajesTEC-1 and MonumenTAL-1 (Ishida 2024, NCT04696809, N=40 participants).[123, 124] Further, 17 real-world evidence studies were also not used in the submission, as they represented a lower grade of empirical evidence.

A risk of bias assessment was conducted on all included studies to standards recommended by NICE. The SLR also adhered to established methods for conducting systematic reviews and was reported in accordance with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.[125]

Full details of the SLR methodology used to identify the clinical evidence relevant to talquetamab in this submission, including the search and PICO strategy, PRISMA flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix B.

2.2 List of relevant clinical effectiveness evidence

The most relevant study identified in the clinical SLR that investigated the efficacy and safety of talquetamab as a treatment for adult patients with TCE RRMM was the MonumenTAL-1 trial, which was formed of two phases, NCT03399799 for Phase I and NCT04634552 for Phase II.

Talquetamab holds a marketing authorisation for use in adult patients with RRMM who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.[1] MonumenTAL-1 was the registrational trial supporting the licence application for talquetamab and therefore forms the principal source of effectiveness data for this submission.[126, 127]

MonumenTAL-1 is an ongoing Phase I/II, open-label, single-arm, multicentre study investigating the safety and efficacy of talquetamab as a monotherapy in adult patients with TCE RRMM.[128, 129] The study commenced in 2018 and is the first in-human Phase I/II study of talquetamab.[128, 129] The data presented in this submission are based on the September 2024 data cut-off (DCO) of MonumenTAL-1, which is the [redacted].[44, 46] An overview of MonumenTAL-1 is presented in Table 4 below.

The MonumenTAL-1 trial comprised several cohorts that included slightly different patient populations and talquetamab dosing regimens. These are discussed further in Section 2.3.1.

Table 4: Clinical effectiveness evidence

Study	MonumenTAL-1 (NCT03399799 for Phase I; NCT04634552 for Phase II)[44, 128, 129]
Study design	A Phase I/II international, open-label, multicentre, single-arm trial assessing the safety and efficacy of talquetamab as a monotherapy consisting of three parts: • Phase I (Part 1): dose escalation • Phase I (Part 2): dose expansion • Phase II (Part 3): patients receiving the recommended phase 2 dose (RP2D) expansion
Population	Adult patients with RRMM who have received previous treatment with an IMiD, PI and anti-CD38 mAb who received talquetamab at the licensed Phase II dose.
Intervention(s)	Phase I (Part 1) dosing:[44] • Talquetamab IV: Dose escalation was initiated at 0.0005 mg/kg, Q2W and was additionally administered at doses ranging from 0.001 to 0.00038 mg/kg Q2W and 0.0015 to 0.18 mg/kg weekly. The majority of the IV doses were preceded by step-up dosing. • Talquetamab SC: Dose escalation was initiated at 0.005 mg/kg weekly and was additionally administered at doses ranging from 0.015 to 0.8 mg/kg weekly, 0.8 or 1.2 mg/kg Q2W, or 1.6 mg/kg monthly. All SC doses were preceded by step-up dosing. Phase I (Part 2) dosing:[44] • A treatment dose of 0.405 mg/kg weekly on Days 1, 8, and 15 of 21-day cycles (preceded by step-up doses of 0.01 and 0.06 mg/kg before Cycle 1 Day 1).[a] • Or a treatment dose of 0.8 mg/kg Q2W on Days 1 and 15 of 28-day cycles (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg before Cycle 1 Day 1). Patients in Part 3 were enrolled in 3 cohorts. Patients in Cohorts A and C had not been exposed to prior TCR therapies such as CAR-T or BsAbs, whilst patients in Cohort B had previously received TCR therapies.[44] Phase II (Part 3) dosing:[44] • Cohort A (not exposed to TCR): 0.4 mg/kg weekly SC on Days 1, 8, 15, and 22 of a 28-day cycle (preceded by step-up doses of 0.01 and 0.06 mg/kg).[a] • Cohort B (prior TCR): 0.4 mg/kg weekly SC on Days 1, 8, 15, and 22 of a 28-day cycle (preceded by step-up doses of 0.01 and 0.06 mg/kg, separated by 2 to 4 days and completed 2 to 4 days before first weekly treatment dose) or 0.8 mg/kg Q2W on Days 1 and 15 of a 28-day cycle (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg, each separated by 2 to 4 days

Study	MonumenTAL-1 (NCT03399799 for Phase I; NCT04634552 for Phase II)[44, 128, 129]
	and completed 2 to 4 days before first weekly treatment dose). • Cohort C (not exposed to TCR): 0.8 mg/kg Q2W on Days 1 and 15 of a 28-day cycle (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg, each separated by 2 to 4 days and completed 2 to 4 days before first Q2W treatment dose). Talquetamab was administered to patients until disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study (defined as two years after the last patient had received the initial dose of talquetamab or when the last patient had completed the last study assessment in the study, whichever occurred first).
Comparator(s)	N/A – At the time of the study initiation date (3rd January 2018), there were no regulatory-approved therapies specifically indicated for patients with TCE RRMM and RWE demonstrated a lack of SoC in this setting.[25] As such, MonumenTAL-1 was designed as a single-arm trial.[44, 128, 129] Single-arm study designs are common in early phase oncology trials, in particular for rare conditions with high unmet needs, such as TCE RRMM. As detailed in Section 1.3.1, patients with TCE RRMM have a poor prognosis, and therefore it would be unethical to withhold an effective treatment option from patients if they were to take part in a placebo-controlled trial. The subsequent regulatory approval of all TCE-indicated therapies (e.g., ide-cel, cilta-cel, teclistamab, talquetamab, etc) has been solely based on pivotal single-arm trials and direct comparative evidence is not yet available for any of these therapies in TCE RRMM treatment.[130-136]
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Reported outcomes specified in the decision problem[c]	• Overall response rate (ORR)
	• **Overall survival (OS)**
	• **Progression-free survival (PFS)**
	• Time-to-next-treatment (TTNT)
	• Other response rates:
	  ○ Duration of response (DoR)
	  ○ Stringent complete response (sCR)
	  ○ Complete response or better (≥CR)
	  ○ Very good partial response or better (≥VGPR)
	• **Adverse events (AEs)**
	• Health-related quality of life (HRQoL) outcomes;[d]
	  ○ European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30)

Study	MonumenTAL-1 (NCT03399799 for Phase I; NCT04634552 for Phase II)[44, 128, 129]
	○ **EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L)** ○ Patient Global Impression of Severity (PGIS)

Footnotes: [a] The RP2D dose of 0.405 mg/kg was adjusted to 0.4 mg/kg for operational convenience.[137] [b] Step-up doses were separated by 2 to 4 days and completed 2 to 4 days before first weekly treatment dose. [c] Bolded outcomes are included in the economic model. [d] Please note that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline and therefore not presented in this section. It will be provided as an addendum when possible.
Abbreviations: AEs: adverse events; CR: complete response; DLT: dose-limiting toxicity; DoR: duration of response; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L: European Quality of Life Five Dimension Five Level Questionnaire; HRQoL: health-related quality of life; IMiD: immunomodulatory drug; IV: intravenous; mAb: monoclonal antibody; MRD: minimal residual disease; N/A: not applicable; NCT: National Clinical Trial; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PGIS: Patient Global Impression of Severity; PI: proteasome inhibitor; Q2W: every two weeks; QW: once weekly; RRMM: relapsed or refractory multiple myeloma; RP2D: recommended phase 2 dose; RWE: real-world evidence; sCR: stringent complete response; SC: subcutaneous; SoC: standard of care; TCE: triple-class exposed; TCR: T-cell redirecting therapy; TTD: time to treatment discontinuation; TTR: time to response; TTNT: time to next treatment; VGPR: very good partial response.
Source: Clinicaltrials.gov. NCT03399799. 2024.[129] Clinicaltrials.gov. NCT04634552. 2024.[128] J&J IM. Data on File. MonumenTAL-1 Protocol. 2022.[44]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design

MonumenTAL-1 (NCT03399799 for Phase I; NCT04634552 for Phase II) forms the principal clinical evidence base for talquetamab in TCE RRMM. MonumenTAL-1 is an ongoing, first-in-human, Phase 1/2, open-label, multicentre trial evaluating the safety, tolerability, pharmacokinetics, and anti-myeloma activity of talquetamab in the treatment of TCE adult patients with RRMM; conducted across 47 centres that treated at least 1 patient in Belgium, France, Germany, Israel, the Netherlands, Poland, Republic of Korea, Spain, and the United States.[44, 128, 129] An overview of the MonumenTAL1 trial design is provided in Figure 6.

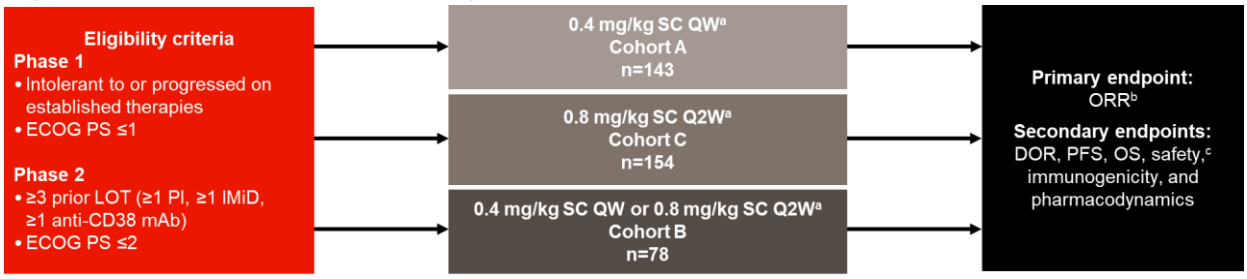
An overview of the primary objectives of the three parts of MonumenTAL-1 is provided below:[46]

Part 1 (dose escalation; Phase 1) to characterise the safety of talquetamab and to identify the recommended phase 2 doses (RP2Ds)

Part 2 (dose expansion; Phase 1) to further characterise the safety of talquetamab at the putative RP2Ds

Part 3 (dose expansion; Phase 2) to evaluate the efficacy of talquetamab at the RP2Ds in cohorts of TCE patients with RRMM who previously received ≥3 prior lines of therapy

Figure 6: MonumenTAL-1 trial design



Footnotes: [a] With 2–3 step-up doses. [b] Assessed by IRC using International Myeloma Working Group criteria. [c] CRS and ICANS were graded by ASTCT criteria; all other AEs were graded by CTCAE v4.03.
Abbreviations: ASTCT: American Society of Transplantation and Cellular Therapy; CD38: cluster of differentiation 38; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; ICANS: immune effector cell–associated neurotoxicity syndrome; IMiD: immunomodulatory drug; IRC: independent review committee; LOT: line of therapy; mAb: monoclonal antibody; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PI: proteasome inhibitor; Q2W: biweekly; QW: weekly; RRMM: relapsed/refractory multiple myeloma; SC: subcutaneous; TCE: triple class exposed; TCR: T-cell redirection therapy.
Source: Rasche *et al.* 2024.[138]

Patient cohorts

In Part 1, a range of escalating dose levels of talquetamab were assessed, administered either intravenously (IV) or subcutaneously (SC). The RP2Ds of 0.4 mg/kg QW SC and 0.8 mg/kg Q2W were selected based on pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data from Part 1 and Part 2. The dosing and schedule of administration in Part 1 and Part 2 are discussed further in Table 6. In Part 3, talquetamab was administered SC at the RP2Ds confirmed in Part 2. These RP2Ds were explored in three cohorts in Part 3 (Phase II), with the results from the combination of Phase I and Phase II patients who specifically received the RP2Ds informing this submission:

- Cohort A (patients without prior TCR exposure) 0.4 mg/kg QW SC talquetamab
- Cohort B (patients with prior TCR exposure): 0.4 mg/kg QW SC or 0.8 mg/kg Q2W SC talquetamab
- Cohort C (patients without prior TCR exposure): 0.8 mg/kg Q2W SC talquetamab

For simplicity, throughout this submission, Cohort A, Cohort B and Cohort C each refer to the combination of patients from Phases I and II of MonumenTAL-1 who received SC talquetamab at the RP2D (i.e., patients from parts 2 and 3).

Of these cohorts, **Cohort C provides the most relevant evidence for talquetamab with respect to the decision problem for this submission**, for the reasons outlined below**.**

The key difference between Cohorts A and C is the dosing regimen of talquetamab. In Cohort A, patients received 0.4 mg/kg talquetamab QW, while in Cohort C, patients received 0.8 mg/kg talquetamab Q2W. Clinical feedback confirmed that the vast majority (90%) of patients in UK clinical practice will likely receive the Q2W regimen with 10% receiving the QW regimen. This is due to the reduced requirement for hospital visits and hence improved convenience over the weekly regimen.[16] This assumption is further supported by the findings from a real-world evidence study (RealiTAL) including 93 patients receiving talquetamab across seven European Countries, where 88% of patients begun their treatment on the biweekly dosing regimen.[15] Furthermore, clinical experts highlighted that Q2W dosing would be preferable given that the overall incidence of treatment-related adverse events (TEAEs) related to talquetamab, serious

TEAEs, serious TEAEs related to talquetamab and Grade 1–3 TEAEs were lower in Cohort C compared to Cohort A (as presented in Section 2.11 and Appendix L). The data in Cohort C are therefore deemed more relevant than Cohort A for decision-making in the UK.

Unlike Cohorts A and C, Cohort B exclusively included patients who had previously received BCMA-targeting TCR therapies. The vast majority of these patients (73.1%) had prior exposure to CAR-T therapies, reflecting the international nature of MonumenTAL-1.[117] Since CAR-T therapies are not currently available to NHS patients with TCE RRMM, this cohort presents limitations for decision making compared to the results from Cohorts A and/or Cohort C. This assessment was corroborated by clinical experts consulted by the Company.

Cohort C therefore represents the main source of evidence for talquetamab in this submission and is the focus of the remaining clinical sections presented below. For completeness, the data from Cohorts A and B in MonumenTAL-1 are presented in Appendix L. A summary of the different patient cohorts in MonumenTAL-1, and where the data have been presented in the submission, is provided in Table 5 below.

Table 5: Patient cohorts in MonumenTAL-1

Patient cohort	Description	Number of patients	Place in submission
Included in the submission			
Cohort C	TCE RRMM patients, not previously treated with TCR, receiving 0.8 mg/kg Q2W talquetamab	154	Section 2.6
Not considered as a relevant patient population in the submission			
Cohort A	TCE RRMM patients, not previously treated with TCR, receiving 0.4 mg/kg QW SC talquetamab	143	Appendix L
Cohort B	TCE RRMM patients, previously treated with TCR, receiving 0.4 mg/kg QW or 0.8 mg/kg Q2W talquetamab[a]	78	Appendix L

Footnotes: [a] Patients in Phase II Cohort B received talquetamab 0.4 mg/kg SC QW, however, here, Cohort B represents the combination of patients from Phase I and Phase II, which also includes patients who received talquetamab at 0.8 mg/kg Q2W in Phase I.
Abbreviations: QW: once weekly; Q2W: every two weeks; RRMM: relapsed or refractory multiple myeloma; SC: subcutaneous; TCE: triple-class exposed; TCR: T-cell redirection.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.3.2 Trial methodology

A summary of the methodology and trial design of MonumenTAL-1 is presented in Table 6.

Table 6: MonumenTAL-1 trial design and methodology

Trial name	MonumenTAL-1
Location	Phase I and Phase II of MonumenTAL-1 were conducted across 47 centres that treated at least 1 patient in Belgium, France, Germany, Israel, the Netherlands, Poland, Republic of Korea, Spain, and the United States.[44]
Trial design	A Phase I/II, first-in-human, open-label, multicentre study of talquetamab monotherapy in patients with RRMM.

Key Inclusion/exclusion criteria	**Inclusion criteria:** • ≥18 years of age • MM must be measurable[a] • Phase 2 Cohorts A and C[b] had received ≥3 prior LOT including at least one IMiD, one PI, and an anti-CD38 mAb (TCE); no exposure to T cell redirection therapies • ECOG PS score of 0 or 1 (Phase 1) or 0 to 2 (Phase 2) **Exclusion criteria:** • Phase 2 patients in Cohorts A and C: exposure to a CAR-T or TCR therapy at any time • Any prior GPRC5D targeting therapy • Prior Grade ≥3 CRS related to any prior TCR therapies • Vaccinated with live, attenuated vaccine within four weeks or as recommended by the product manufacturer prior to the first dose, during treatment, or within 100 days of the last dose of talquetamab • Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less, except for alopecia or peripheral neuropathy • Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug (does not include pre-treatment medication) • Phase 2: stroke or seizure within six months prior to signing the informed consent form (ICF)
Method of study drug administration	**Dose and route/regimen** Talquetamab is administered at a RP2D dose of 0.4 mg/kg QW SC or 0.8 mg/kg Q2W. • Patients were monitored before and after administration according to the trial protocol **Dosing instructions** Part 1 (Phase 1 dose escalation): talquetamab was administered by IV or SC routes in multiple dose cohorts. Part 2 (Phase 1 dose expansion): talquetamab was administered SC at the putative RP2Ds identified in Part 1. Part 3 (Phase 2): talquetamab was administered SC at the 2 RP2Ds confirmed in Part 2. **Schedule of administration** • **Part 1 (Phase la dose escalation) step-up dose schedule**: ○ Dose escalation for talquetamab IV was initiated at 0.0005 mg/kg Q2W. Talquetamab IV was additionally administered at doses ranging 0.001 to 0.00338 mg/kg Q2W and 0.0015 to 0.180 mg/kg weekly. The majority of IV doses were preceded by step-up dosing. ○ Dose escalation for talquetamab SC was initiated at 0.005 mg/kg weekly. Talquetamab SC was additionally administered at doses ranging from 0.015 to 0.8 mg/kg weekly, 0.8 or 1.2 mg/kg Q2W, or 1.6 mg/kg monthly. All SC doses were preceded by step-up dosing. • **Part 2 (Phase la dose expansion):** A treatment dose of 0.405 mg/kg weekly on Days 1, 8, and 15 of 21-day cycles (preceded by step-up doses of 0.01 and 0.06 mg/kg before Cycle 1 Day 1); or a treatment dose of 0.8 mg/kg Q2W on Days 1 and 15 of 28-day

	cycles (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg before Cycle 1 Day 1). • **Part 3 (Phase IIb):** In Cohort A, the step-up schedule was talquetamab SC at 0.01 and 0.06 mg/kg, separated by 2 to 4 days and to be completed 2 to 4 days before the first weekly treatment dose of 0.4 mg/kg. In this part of the study, the RP2D dose of 0.405 mg/kg was adjusted to 0.4 mg/kg for operational convenience. ○ The treatment dose schedule for Cohort A was Days 1, 8, 15, and 22 of a 28-day cycle. In Cohort C, the step-up schedule was talquetamab SC at 0.01, 0.06, and 0.3 mg/kg, each separated by 2 to 4 days and to be completed 2 to 4 days before the first Q2W treatment dose of 0.8 mg/kg. The treatment dose schedule for Cohort C was Days 1 and 15 of a 28-day cycle.
Primary outcomes	• ORR (defined as the proportion of patients who achieve PR or better according to IMWG criteria,[139] as assessed by the independent review committee).
Secondary and exploratory outcomes reported in this submission[d]	**Secondary outcomes reported in this submission:** • DoR • ≥VGPR • ≥CR • sCR • TTR • PFS • TTNT • OS • MRD negativity rate • Number of patients with AEs • Number of patients with SAEs • Change from baseline in HRQoL as measured by EORTC QLQ-C30[e] • Change from baseline in HRQoL as measured by EQ-5D-5L[e] • Change from baseline in HRQoL as measured by PGIS[e]
Pre-planned subgroups	• Sex (male versus female) • Age • Baseline renal function • Race • Baseline ECOG performance score (0 versus ≥1) • Number of lines of prior therapy (<4 versus ≥4) • Refractory to: ○ Last line of prior therapy ○ PI+IMiD ○ PI+IMiD plus anti-CD38 mAb ○ At least two PIs plus at least 2 IMiDs plus one anti-CD38 mAb • Prior autologous stem cell transplant (yes versus no) • Type of myeloma (IgG versus non-IgG) • Baseline International Staging System (ISS) • Baseline revised ISS (R-ISS) • Baseline tumour GPRC5D expression (≥ median value versus < median value)

	• Prior ADC (yes versus no) • Cytogenetic risk (high-risk[c] versus standard-risk) • Bone marrow % plasma cells (≤30, >30–<60, ≥60) • Prior lines of therapy and refractory status (≥4 lines of therapy and triple refractory) • Baseline extramedullary plasmacytomas (0 or ≥1)
Duration of study and follow-up	The first patient in the study was treated on 3rd January 2018 (which corresponds to the date the first patient signed the informed consent form, Part 1) and at the latest DCO the median duration of follow-up was 38.2, 30.3 and 31.2 months for Cohorts A, B and C respectively.

Footnotes: [a] Additional criteria for Parts 2 and 3: 1) serum monoclonal paraprotein (M-protein) levels ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or 2) light chain multiple myeloma without measurable disease in the serum or urine (serum immunoglobulin FLC ≥10 mg/dL and abnormal se rum immunoglobulin kappa lambda FLC ratio).
[b] Cohort A received talquetamab at the RP2D of 0.4 mg/kg QW SC; Cohort C received talquetamab at the RP2D of 0.8 mg/kg Q2W.
[c] High risk is defined by participants having t (4; 14); t (14; 16) and/or 17p deletion.
[d] Outcomes not reported in this submission can be found in the MonumenTAL-1 2024 CSR that accompanies this submission.
[e] Please note that the write-up of the PRO data from the September 2024 DCO was not available in time for the submission deadline. It will be provided as an addendum when possible.
The RP2D 0.4 mg/kg QW SC and RP2D 0.8 mg/kg Q2W cohorts maybe of relevance to this submission. The efficacy results of patients receiving RP2D 0.8 mg/kg Q2W but who had prior exposure to T cell redirection therapies were excluded from this submission given this cohort does not form part of license.
Abbreviations: AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; CR: complete response; CRS: cytokine release syndrome; DoR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D-5L: EuroQoL 5 Dimensions, 5 Levels; HRQoL: health-related quality of life; ICANS: immune effector cell-associated neurotoxicity syndrome; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events ; OS: overall survival; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PGIS: Patient Global Impression of Severity; PR: partial response; SAE: serious adverse event; sCR: stringent CR; TTNT: time to next treatment; TTR: time to response; UK: United Kingdom; VGPR: very good partial response.
Source: Clinicaltrials.gov. Dose Escalation Study of Talquetamab in Patients with Relapsed or Refractory Multiple Myeloma (MonumenTAL-1). 2024.[129] Clinicaltrials.gov. A Study of Talquetamab in Patients with Relapsed or Refractory Multiple Myeloma (MonumenTAL-1).[128] J&J IM. Data on File. MonumenTAL-1 HEMAR report (January 2024 DCO).[140] Rasche, *et al.* 2025.[119]

2.3.3 Baseline Characteristics

Data presented in this section are based on patients from Cohort C (0.8 mg/kg Q2W [N=154]) in the MonumenTAL-1 clinical trial, from the September 2024 DCO. A summary of baseline demographic and disease characteristics of these patients is provided in Table 7. A summary of prior treatment history for patients in Cohort C is provided in Table 8. For completeness, the baseline characteristics and prior treatments for patients in Cohort A (0.4 mg/kg SC QW) and Cohort B (Prior TCR) are presented in Appendix L.

The median age of patients in Cohort C was 67.0 years (range, [redacted]), with [redacted]% of patients aged <65 years.[46, 117] Overall, 58.4% of patients were male, and the majority of patients were white ([redacted]%). The median time from diagnosis of MM to first dose of talquetamab in this patient cohort was 6.28 years (range, [redacted]).[46, 117] The majority of patients (69.9%) had standard cytogenetic risk, while the remaining 30.1% were considered high risk.[117] Of the [redacted] patients ([redacted]%) for whom R-international staging system (ISS) staging was known, [redacted]% of patients' disease was Stage II, with [redacted]% of patients having Stage I disease, and the remaining [redacted]% of patients experiencing R-ISS Stage III disease.[46]

All patients in MonumenTAL-1 were triple class exposed in line with the marketing authorisation for talquetamab, with a median of 4.5 previous lines of therapy (range, [redacted]) in Cohort C.[1, 46, 117] Approximately 69.5% of patients were penta-drug exposed, meaning they had received at least two IMiDs, at least two PIs, and at least one anti-CD38 mAb.[117] Due to the international context of the MonumenTAL-1 trial, prior therapies received by patients in MonumenTAL-1 may not fully reflect the NHS treatment landscape for multiple myeloma. However, as increasing lines of prior therapy is known to be associated with a worsened symptom burden, prognosis and response to treatment, the efficacy data observed in the MonumenTAL-1 trial is highly likely to represent a conservative underestimate of the 'true' efficacy of talquetamab in less pretreated TCE RRMM patients seen within NHS cancer services.[24, 25]

Compared to the patient population in MajesTEC-1, which was accepted for decision making in TA1015, there are minimal differences in the prior therapies received and refractory status of patients in MonumenTAL-1.[3, 141, 142] The average age of patients in MonumenTAL-1 and MajesTEC-1 were similar, with a median age of 67.0 and 64.0 years, respectively.[117, 143] However, the patient population in MonumenTAL-1 had a greater proportion of patients aged ≥75 than MajesTEC-1 ([redacted]% compared to 14.5%, respectively).[46, 143] In addition to this, MonumenTAL-1 included a higher proportion of patients with ISS stage III disease (24.4% compared to 12.3% for MonumenTAL-1 and MajesTEC-1, respectively) and extramedullary plasmacytomas (26.6% had ≥1 compared to [redacted]% in MonumenTAL-1 and MajesTEC-1, respectively), together suggesting that the population of patients receiving talquetamab are harder to treat and have more advanced disease than those receiving teclistamab in MajesTEC-1, and is more reflective of UK clinical practice.[117, 141, 142]

The generalisability of the MonumenTAL-1 trial population to UK clinical practice was further informed and confirmed by discussions with UK clinical experts.

- Clinical experts considered that, while there are some differences, on balance, the baseline disease characteristics of patients in Cohort C in MonumenTAL-1 were generally aligned with characteristics of patients with 4L+ TCE RRMM in UK clinical practice. For example, 24.2% of patients in Cohort C had ISS Class III disease, which aligns with the estimate of a third of patients in UK clinical practice having ISS Class III.[117]
- Clinical experts considered that the MonumenTAL-1 population was younger (median age of 67.0 years) compared to UK clinical practice (in which the majority of patients may be aged over 70).[117] However, experts also emphasised that, while young, the median age was comparable to recent clinical trials for innovative therapies for TCE RRMM, including MajesTEC-1, as described above, but also MagnetisMM-3 for elranatamab and the STORM trial for SelDex, in which median age was 68.0 years and 65.2 years respectively.[6, 142, 144] As MajesTEC-1 was considered an appropriate source of evidence for decision making for teclistamab as part of TA1015, MagnetisMM-3 and STORM an appropriate source for decision making respectively for Elranatamab in TA1023 and for SelDex in TA970, the age of patients in MonumenTAL-1 should not be considered to represent a major source of uncertainty.[3, 6, 40]
- Clinical experts noted that there was a higher proportion of males (58.4% in Cohort C), and that an additional strength of the trial was that the racial distribution of patients in the MonumenTAL-1 trial was more diverse than would be expected in UK clinical practice,

thus ensuring that the results of MonumenTAL-1 are relevant to patients across different ethnic groups.[117]

Table 7: Baseline characteristics and demographics in MonumenTAL-1 (Cohort C [0.8 mg/kg Q2W])

Baseline Characteristic	Cohort C (0.8 mg/kg Q2W) [N=154]
Age, years	154 (100.0%)
<65 years, n (%)	[redacted]
65 - <75 years, n (%)	[redacted]
≥75 years, n (%)	[redacted]
Mean (SD)	[redacted]
Median (range)	67.0 [redacted]
Sex, n (%)	154 (100.0%)
Female	64 (41.6%)
Male,	90 (58.4%)
Race, n (%)	154 (100.0%)
Asian	6 (3.9%)
Black or African American	17 (11.0%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)
White	126 (81.8%)
Multiple	1 (0.6%)
Unknown	1 (0.6%)
Not reported	2 (1.3%)
Ethnicity, n (%)	[redacted]
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Not reported	[redacted]
Weight, kg (%)	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
ECOG Performance Status score prior to infusion, n (%)	154 (100.0%)
0	58 (37.7%)
1	84 (54.5%)
2	12 (7.8%)
Type of myeloma by immunofixation or serum FLC assay, n (%)	[redacted]
IgG	[redacted]
IgA	[redacted]
IgM	[redacted]
IgD	[redacted]
IgE	[redacted]
Light chain	[redacted]
Kappa	[redacted]

Baseline Characteristic	Cohort C (0.8 mg/kg Q2W) [N=154]
Lambda	[redacted]
FLC-Kappa[a]	[redacted]
FLC-Lambda[b]	[redacted]
Biclonal	[redacted]
Negative immunofixation	[redacted]
Type of measurable disease, n (%)	[redacted]
Serum only	[redacted]
Serum and urine	[redacted]
Urine only	[redacted]
Serum FLC	[redacted]
Not evaluable	[redacted]
ISS Staging, n (%)[c]	153 (99.4%)
Stage I	68 (44.4%)
Stage II	48 (31.4%)
Stage III	37 (24.2%)
R-ISS Staging, n (%)[d]	[redacted]
Stage I	[redacted]
Stage II	[redacted]
Stage III	[redacted]
Time from MM diagnosis to first dose, years	154 (100.0%)
Mean (SD)	[redacted]
Median (range)	6.28 [redacted]
Number of lytic bone lesions, n (%)	[redacted]
None	[redacted]
1−3	[redacted]
4−10	[redacted]
More than 10	[redacted]
Number of extramedullary plasmacytomas, n (%)[e]	154 (100.0%)
0	113 (73.4%)
≥1	41 (26.6%)
Plasma cells, bone marrow biopsy/aspirate, n (%)[f]	150 (97.4%)
<5	[redacted]
≥5 – ≤30	[redacted]
>30 – <60	[redacted]
≥60	34 (22.7%)
Cytogenetic risk, n (%)	133 (86.4%)
Standard risk	93 (69.9%)
High risk	40 (30.1%)
del(17p)	[redacted]
t(4;14)	[redacted]
t(14;16)	[redacted]

Baseline Characteristic	Cohort C (0.8 mg/kg Q2W) [N=154]
Bone marrow cellularity biopsy, n (%)	[redacted]
Hypercellular	[redacted]
Normocellular	[redacted]
Hypocellular	[redacted]
Indeterminate	[redacted]
Tumour GPRC5D expression	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]

Footnotes: [a] Includes patients without a positive immunofixation but with evidence of free light chain kappa by FLC testing. [b] Includes patients without a positive immunofixation but with evidence of free light chain lambda by FLC testing. [c] ISS staging is derived based on serum β2-microglobulin and albumin. [d] R-ISS is derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level (LDH). [e] Extramedullary disease was exclusively defined by the presence of extramedullary soft tissue lesions. In contrast, other studies include patients with soft tissue or paraskeletal lesions in this subgroup; these patients historically have better outcomes than patients with soft tissue plasmacytomas. [f] Maximum value from bone marrow biopsy or bone marrow aspirate is selected if both the results are available.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; FLC: free light chain; Ig: immunoglobulin; IMiD: immunomodulatory drug; ISS: International Staging System; mAb: monoclonal antibody; MM: multiple myeloma; PI: proteasome inhibitor.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Chari *et al.* 2025.[117]

Table 8: Prior therapies in MonumenTAL-1 (Cohort C [0.8 mg/kg Q2W])

	Cohort C (0.8 mg/kg Q2W) [N=154]
Number of prior LOT, n (%)	154 (100.0%)
2[a]	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
>5	[redacted]
Mean (SD)	[redacted]
Median (range)	4.5 [redacted]
Prior PI, n (%)[b]	154 (100.0%)
Prior IMiD, n (%)[c]	154 (100.0%)
Prior anti-CD38, n (%)[d]	154 (100.0%)
Prior other therapies, n (%)	[redacted]
Prior Selinexor	[redacted]
Prior Melphalan Flufenamide	[redacted]
Prior Belantamab	17 (11%)
Prior Elotuzumab	[redacted]
Prior Panobinostat	[redacted]
Prior PI+IMiD	[redacted]
Prior PI+IMiD+anti-CD38	154 (100.0%)
Prior penta-exposed[e]	107 (69.5%)
Prior transplantation, n (%)	121 (78.6%)

	Cohort C (0.8 mg/kg Q2W) [N=154]
Autologous	[redacted]
1	[redacted]
≥ 2	[redacted]
Allogenic	[redacted]
Prior cancer treatment, n (%)	[redacted]
Prior radiotherapy	[redacted]
Prior cancer-related surgery/procedure	[redacted]

Footnotes: [a] The patients with only two prior LOT were from Phase I of MonumenTAL-1 which did not require patients to be TCE; [b] PI includes bortezomib, carfilzomib, ixazomib; [c] IMiD includes thalidomide, lenalidomide, and pomalidomide; [d] anti-CD38 includes daratumumab and isatuximab; [e] Penta includes at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
Percentages calculated with the number of all treated patients as denominator.
Abbreviations: IMiD: immunomodulatory drug; LOT: line of therapy; PI: proteasome inhibitor; SD: standard deviation.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Chari *et al.* 2025.[117]

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Study population and patient disposition

The population of patients in MonumenTAL-1 used to inform the efficacy evidence in this submission is Cohort C (0.8 mg/kg Q2W talquetamab [N=154]), with a clinical data cut-off date of September 2024. A table of the study disposition in Cohort C in MonumenTAL-1, from the September 2024 DCO is provided in Table 9, and a summary of the treatment disposition is provided in Table 10. At the clinical cutoff, [redacted]% of participants had discontinued study participation including [redacted]% who had completed the study at the time of death.[46] As of the September 2024 DCO, 17.5% of patients remained on talquetamab treatment.[46, 119] The primary reason for talquetamab discontinuation was due to progressive disease ([redacted]%), with [redacted] patients ([redacted]%) discontinuing talquetamab due to adverse events. [redacted] patients ([redacted]%) died during follow-up.[46]

Table 9: Study disposition; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

Study disposition	Responders in Cohort C (0.8 mg/kg Q2W)
Discontinued the study	[redacted]
Reason for discontinuation	
Death	[redacted]
Withdrawal by patient	[redacted]
Start of subsequent anticancer therapy	[redacted]
Lost to follow-up	[redacted]

Footnotes: [a] Patient refused further treatment includes "Withdrawal by patient" from Phase 1 RP2D.
Abbreviations: Q2W: once every other week.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

Table 10: Treatment disposition; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

Treatment disposition	Responders in Cohort C (0.8 mg/kg Q2W)
Patients who are still on treatment	27 (17.5%)
Patients who discontinued study drug	[redacted]
Reason for discontinuation	
Progressive disease	[redacted]
Physician decision	[redacted]
Adverse event	[redacted]
Patient refused further treatment[a]	[redacted]
Death	[redacted]

Footnotes: [a] Patient refused further treatment includes "Withdrawal by patient" from Phase 1 RP2D.
Abbreviations: Q2W: once every other week.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

2.4.2 Statistical analysis

Analysis sets

A summary of the analysis sets in MonumenTAL-1 are presented in Table 11.

The overall analysis set defined in the MonumenTAL-1 trial was termed the 'All Treated Analysis Set'. This consisted of all N=375 patients split across Cohorts A (0.4 mg/kg SC QW), B (Prior TCR) and C (0.8 mg/kg Q2W), as outlined in Section 2.3.1. However, for the reasons previously detailed in Section 2.3.1, Cohorts A and B are deemed less relevant to the decision problem of this submission. As such, this submission focuses on Cohort C as the main source of evidence for talquetamab from the MonumenTAL-1 trial.

Within Cohort C, there are two different analysis sets that are of relevance to this submission:

1) A total of 154 patients were included in Cohort C and received at least 1 dose of talquetamab. This total population of patients is used to inform the main source of efficacy and safety data for talquetamab within this submission,

2) A subset of patients included in the Phase II portion of the study in Cohort C was used to inform the analysis of PROs, as PROs were not assessed during the Phase I portion of the study.

Table 11: Summary of relevant analysis sets in MonumenTAL-1

Analysis Set	MonumenTAL-1	Number of patients
Relevant to submission		
(Cohort C [0.8 mg/kg Q2W])	This analysis set consists of all patients who received at least 1 dose of talquetamab. This analysis set will be used for safety and efficacy summaries. Of the patients in the All Treated Analysis Set, only patients in Cohort C (0.8 mg/kg Q2W) are of relevance to this submission.	N=154

PRO Analysis Set (Cohort C [0.8 mg/kg Q2W])	Patients enrolled in Phase II of the study, within Cohort C. PROs were not assessed in Phase I.	See footnote[a]

Footnotes: [a] Please note that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline and therefore not presented in this section. It will be provided as an addendum when possible.
Abbreviations: DLT: dose limiting toxicity; PRO: patient reported outcome; Q2W: once every 2 weeks; SC: subcutaneous.
Source: J&J IM. Data on File. MonumenTAL-1 Study Protocol.[44]

Details of the statistical methods for both the Phase I and Phase II primary analyses in MonumenTAL-1 are presented in Table 12.

Table 12: Statistical methods for the primary analysis of MonumenTAL-1

Trial name	MonumenTAL-1
Hypothesis objective	Part 1 (Dose escalation): one or more proposed RP2D(s) of talquetamab, which are safe and tolerable, can be identified such that <28% of the patients experience a DLT. Part 2 (Dose expansion): talquetamab is biologically active and safe at the proposed RP2D(s). Part 3 (Phase 2 dose expansion): talquetamab has anti-myeloma activity and demonstrates acceptable safety in 1 or more of 2 cohorts of patients with relapsed or refractory multiple myeloma with unmet medical need that differ by previous therapy: ○ Cohort A: treatment with talquetamab will have significant anti-myeloma activity (i.e., the lower limit of two-sided 95% confidence interval [CI] for ORR is greater than 30%). ○ Cohort B: treatment with talquetamab will have significant anti-myeloma activity (i.e., the lower limit of two-sided 95% CI for ORR is greater than 15%). ○ Cohort C: treatment with talquetamab will have significant anti-myeloma activity (i.e., the lower limit of the two-sided 95% CI for ORR will be greater than 30%).
Statistical analysis	Analysis of the primary endpoint, ORR, was based on the 'all treated analysis set'. Patients with no post-baseline data were considered as non-responders. Response after the start of subsequent therapy was not considered. The ORR and its 2-sided 95% exact CI for each cohort were presented. A forest plot of subgroup analysis on ORR was presented in Section 2.8. Sensitivity analyses of ORR were performed using disease response based on a computerized algorithm and investigator assessment according to IMWG response criteria.[139] The kappa statistics and 95% CI were calculated for agreement between IRC assessment and computerised algorithm assessment for response (response [PR or better] vs. no response). The key secondary efficacy endpoints included DoR, VGPR or better/CR or better/sCR as defined by the IMWG response criteria, TTR, PFS, OS, MRD negativity status, ORR in patients with high-risk molecular features.[139] TTNT was also assessed as an exploratory endpoint, in which the Kaplan-Meier method was used for descriptive summaries. DoR ○ The distribution of DoR was estimated using the Kaplan-Meier method. ≥VGPR rate, ≥CR rate, sCR rate and ORR in patients with high risk. Time to response ○ Time to first response was analysed for patients in who achieved a response (PR or better), and descriptive statistics (N, mean, SD, median, and range) were provided for each cohort. Time to best

	response, time to CR or better response, and time to VGPR or better response were summarised similarly. Analysis was performed based on IRC assessment. PFS ○ Analysis of PFS was based on the 'all treated analysis set'. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each cohort. The median PFS with 95% CI was provided. OS ○ Overall survival was analysed using similar statistical methods as described for PFS analysis. MRD-negative rate ○ The analysis was based on the 'all treated analysis set'. The MRD negative rate and its 2-sided 95% exact CI were presented for each cohort. The threshold value of 10^{-5} was used for the primary MRD negativity analysis. Sensitivity analysis may have been performed with a threshold at 10^{-6}. Exploratory endpoint analysis (TTNT) ○ For this time to event endpoint, the Kaplan-Meier method was used for descriptive summaries. Safety analyses ○ All safety analyses were based on 'all treated analysis set', unless otherwise specified. ○ Descriptive statistics for study medication administration duration (N, mean, SD, median, and range (minimum, maximum)) were presented by cohort for 'all treated analysis set'. Subgroup results for ORR were stratified by using the appropriate statistical methods (e.g., parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint) HRQoL assessments were analysed using descriptive statistics.
Sample size, power calculation	In Part 1 of MonumenTAL-1, one or more patients were enrolled at a dose level with at least 6 patients enrolled at the safe candidate RP2D(s). SC dosing was initiated in addition to IV dosing.[145] In Part 2, up to 40 patients were treated at each of the putative RP2D(s) (if more than one was evaluated) in the expansion part to further assess its safety as well as the preliminary antitumor activity of talquetamab.[145] In Part 3 (Phase 2), each patient was assigned either to Cohort A or Cohort B, based on the patient's prior therapies, or to Cohort C based on prior therapies and cohort availability.[145] ○ The sample size for Cohort A was determined by assuming that the ORR for talquetamab for patients in Cohort A was at least 45%. If that assumption was true, there would be approximately 90% power or greater to declare that the ORR was higher than 30% at the one-sided significance level of 0.025. The ORR calculation in Part 3 included all talquetamab-treated patients in each cohort (patients whose

	response was not evaluable were considered as not having responded for the purposes of the ORR calculation).[145] ○ The sample size for Cohort B was determined by using a 2-stage design to test the null hypothesis that the ORR was at most 15%, against the alternative that the ORR was at least 35%. With a one-sided significance level of 0.025 and a power of 80%, Cohort B needed 34 response-evaluable patients. Assuming a non-evaluable rate of 10%, a total sample size required for Cohort B was 38 patients. The sample size was increased to at least 60 patients to determine the ORR with more precision, i.e., tighter confidence intervals.[145] ○ The sample size for Cohort C was determined by assuming that the observed ORR for talquetamab was at least 45%. If that assumption was true, there would be more than 85% power to declare that the ORR was higher than 30% at the one-sided significance level of 0.025.[145]
Data management, patient withdrawals	**Discontinuation and withdrawal from the study** If a patient discontinued study drug and withdrew from the study, end of treatment assessments were obtained. The primary reason(s) a patient discontinued treatment was recorded on the electronic case report form (eCRF) and source documents. Once a patient discontinues treatment, the patient may not have been re-treated with the study drug in the study. If a patient was lost to follow-up, every reasonable effort had to be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow-up were documented. When a patient withdrew before completing the study, the reason for withdrawal was documented in the eCRF and in the source document. Study drug assigned to the withdrawn patient could not be assigned to another patient. Patients who withdrew for reasons other than toxicity were replaced at the discretion of J&J IM. **Data censoring was applied for the outcomes analysis as follows:** DoR: For patients who did not progress or have died due to causes other than disease progression, data was censored at the last disease evaluation before the start of any subsequent therapy. TTR: For patients without response, data was censored either at the date of progressive disease, or in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy. PFS: For patients who have not progressed and are alive, data was censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Additionally, patients without any post-baseline disease assessment were censored at the date of first dose of study medication administration. OS: If the patient was alive or the vital status was unknown, then the patients' data was censored at the date the patient was last known to be alive.

Abbreviations: CR: complete response; CRS: cytokine release syndrome; DLT: dose-limiting toxicity; DoR: duration of response; eCRF: electronic case report form; HRQoL: health-related quality of life; ICANS: immune effector cell-associated neurotoxicity syndrome; IMWG: International Myeloma Working Group; IRC: independent review committee; IRR: infusion-related reaction; ISRs: injection site reactions; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RP2D: recommended phase 2 dose; sARRs: systemic administration reactions; sCR: stringent complete response; SD: standard deviation; SPM: second primary malignancy; TTR: time to response; TTNT: time to next treatment; VGPR: very good partial response; TLS: tumor lysis syndrome.
Source: J&J IM. Data on File. MonumenTAL-1 Study Protocol;[44] J&J IM. Data on File. MonumenTAL-1 Statistical Analysis Plan.[145]

Definitions of outcome measures

A variety of outcomes were employed in MonumenTAL-1 to explore the efficacy of talquetamab in adult patients with TCE RRMM. Definitions for these outcome measures are presented in Table 13.

Table 13: Definitions for outcome measures used in MonumenTAL-1

Endpoint	Description
Primary Endpoint	
ORR	Defined as the proportion of patients who achieve PR or better according to IMWG criteria,[139] as assessed by the independent review committee.
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,[139] or death due to any cause, whichever occurs first.
VGPR or better	Defined as the proportion of patients who achieve a VGPR or better response according to the IMWG criteria.[139]
CR or better	Defined as the proportion of patients who achieve a CR or better response according to the IMWG criteria.[139]
sCR	Defined as the proportion of patients who achieve a sCR according to the IMWG criteria.[139]
TTR	Defined as the time between date of first dose of talquetamab and the first efficacy evaluation that the patient has met all criteria for PR or better.
MRD-negativity rate	Defined as the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} and 10^{-6} at any timepoint after initial dose of talquetamab and before disease progression or starting subsequent therapy. MRD negativity rate was also summarized for patients who achieved CR/sCR. In addition, the MRD negative CR or better rate, defined as patients in the achieving MRD negative and CR/sCR by IRC, was summarised as well.
PFS	Defined as the time from the date of first dose of talquetamab to the date of first documented disease progression, as defined in the IMWG criteria,[139] or death due to any cause, whichever occurs first. In addition, the number and percentage of patients who had a PFS event or were censored were reported. The reasons for PFS censoring were summarised accordingly. The Kaplan-Meier PFS curve was also plotted. Analysis was performed based on IRC assessment.
OS	Defined as the time from the date of first dose of talquetamab 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.
Occurrence and severity of AEs	An AE is defined is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. All reported treatment-emergent adverse events were included in the analysis. Adverse events of special interest included CRS, and neurotoxicity Grade ≥2 (i.e., ICANS, symptoms of ICANS, and non-ICANS neurotoxicity). Adverse events of clinical interest included tumour lysis syndrome,

Endpoint	Description
	cytopenias (anaemia, neutropenia, thrombocytopenia, lymphopenia), infections (including opportunistic infections and viral infections), infusion-related reactions (IRRs)/systemic administration reactions (sARRs), local injection site reactions (ISRs), hypogammaglobulinemia, immune-mediated/autoimmune disorders, second primary malignancies, skin toxicity, nail disorders, and oral toxicity.
Occurrence and severity of SAEs	A SAE is defined based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use.[146]
Change from baseline in HRQoL as measured by EORTC QLQ-C30	Measures 5 functional scales, 1 global health status scale, 3 symptom scales, and 6 single symptom items. The item and scale scores are transformed to a 0 to 100 scale. Higher scores on functional and global health scales represent greater HRQoL and better functioning, whereas a higher score on symptom scales represents more (worse) symptoms.
Change from baseline in HRQoL as measured by EQ-5D-5L	A total utility score was reported based on the health status, ranging from 0 to 1, where higher values indicated better health utility.
Change from baseline in HRQoL as measured by PGIS	A single item that assesses severity of the patient's health state, on a 5-point verbal rating scale. Response on the PGIS will be used as an anchor to determine meaningful change thresholds and interpretation of results for the EORTC QLQ-C30.
Exploratory Endpoints	
TTNT	Defined as the time from the date of first dose of study drug to the start of the next line treatment. Note that TTNT represents a distinct endpoint to time to subsequent anti-myeloma therapy defined in the MonumenTAL-1 CSR, which includes radiotherapy and does not include deaths due to AEs.

Footnotes: [a] Events of CRS in Phase 1 of the study were graded according to the CRS revised grading system described by Lee, Gardner, Porter, Louis, Ahmed, Jensen, Grupp and Mackall [147]; the ASTCT guidelines, as described by Lee, Santomasso, Locke, Ghobadi, Turtle, Brudno, Maus, Park, Mead, Pavletic, Go, Eldjerou, Gardner, Frey, Curran, Peggs, Pasquini, DiPersio, van den Brink, Komanduri, Grupp and Neelapu [148], were used to grade CRS and ICANS events in Phase 2 of the study.

Abbreviations: AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; CR: complete response; CRS: cytokine release syndrome; DoR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D-5L: EuroQoL 5 Dimensions, 5 Levels; HRQoL: health-related quality of life; ICANS: immune effector cell-associated neurotoxicity syndrome; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events ; OS: overall survival; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival; PGIS: Patient Global Impression of Severity; PR: partial response; SAE: serious adverse event; sCR: stringent CR; TTNT: time to next treatment; TTR: time to response; UK: United Kingdom; VGPR: very good partial response.

Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of MonumenTAL-1, the principal evidence base for talquetamab, was conducted using the modified Downs and Blacks checklist for non-randomised trials.[149] This modified checklist contained 27 questions, covering the concepts of study reporting, external validity, bias, confounding, and power. The results from the quality assessment are presented in Table 14. Overall, MonumenTAL-1 trial represents a robust data source to inform the clinical effectiveness evidence of talquetamab in adult patients with TCE RRMM, with low risk of bias

assessed across majority of the domains. Of those marked as high risk, the majority of these were factors inherent to the design of a single-arm trial – for example, blinding patients/clinicians to the trial intervention in a single-arm would not be feasible

Table 14: Critical appraisal of the non-randomised trials and observational studies included in the clinical SLR update, using the modified Downs and Black checklist

Study	Domain and Question																			
	Reporting										External validity			Outcome						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
MonumenTAL-1 NCT03399799/ NCT04634552	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	HR	HR	LR	LR	LR	LR	LR

Study	Domain and Question						
	Internal validity (confounding)						Power
	21	22	23	24	25	26	27
MonumenTAL-1 NCT03399799/ NCT04634552	LR	NA	HR	NA	NA	LR	LR

Footnotes: *Reporting*: **1)** Is the hypothesis/aim/objective of the study clearly described? **2)** Are the main outcomes to be measured clearly described in the Introduction or Methods section? **3)** Are the characteristics of the patients included in the study clearly described? **4)** Are the interventions of interest clearly described? **5)** Are the distributions of principal confounders in each group of patients to be compared clearly described? **6)** Are the main findings of the study clearly described? **7)** Does the study provide estimates of the random variability in the data for the main outcomes? **8)** Have all important adverse events that may be a consequence of the intervention been reported? **9)** Have the characteristics of patients lost to follow-up been described? **10)** Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is < 0.001? *External validity*: **11)** Were the patients asked to participate in the study representative of the entire population from which they were recruited? **12)** Were those patients who were prepared to participate representative of the entire population from which they were recruited? **13)** Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? *Outcome:* **14)** Was an attempt made to blind study patients to the intervention they have received? **15)** Was an attempt made to blind those measuring the main outcomes of the intervention? **16)** If any of the results of the study were based on "data dredging", was this made clear? **17)** In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? **18)** Were the statistical tests used to assess the main outcomes appropriate? **19)** Was compliance with the intervention/s reliable? **20)** Were the main outcome measures used accurate (valid and reliable)? **21)** Were the patients in different intervention groups recruited from the same population? **22)** Were study patients in different intervention groups recruited over the same period of time? **23)** Were study patients randomised to intervention groups? **24)** Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? **25)** Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? **26)** Were losses of patients to follow-up taken into account? *Power:* **27)** Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?
Abbreviations: HR: high risk of bias; LR: low risk of bias; NA: not applicable.

2.6 Clinical effectiveness results of the relevant studies

The MonumenTAL-1 trial provides the most robust evidence for the clinical efficacy and safety of talquetamab for patients with TCE RRMM that is generalisable to UK clinical practice

- The efficacy of talquetamab in TCE RRMM patients has been demonstrated in MonumenTAL-1, a first-in-human, Phase I/II, ongoing trial.[44] The results presented in the sections below are based on the most recent September 2024 DCO ([redacted]) for Cohort C, with a median follow-up of 31.2 months.[46, 119] As discussed in Section 2.3.1, Cohort C provides the most relevant evidence for talquetamab with respect to the decision problem for this submission.

Talquetamab provides a very high overall response rate among patients with TCE RRMM - amongst the highest recorded for existing MM treatments

- The importance of achieving a response is well documented in the literature, with disease control highlighted as the most important attribute for a MM treatment by patients in a 2019 Myeloma UK study.[126]
- The primary endpoint used in MonumenTAL-1 was ORR, defined as the proportion of patients who achieved PR or better according to the IMWG criteria,[118] as assessed by independent IRC. Over two thirds of patients responded to treatment with talquetamab, with an ORR of 69.5%.[119]
  - The ORR associated with talquetamab is considered to represent the highest magnitude of clinical benefit that can be achieved in orphan disease such as TCE RRMM based on the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies.[150]

The responses were deep and rapid in patients who responded to treatment, thereby providing patients with a renewed sense of hope that their remission will be sustained

- A ≥CR was reported in 40.3% of patients, with 31.2% of patients achieving a sCR and 9.1% of patients achieving a CR, demonstrating that talquetamab provides both a high response rate and responses that are deep and clinically meaningful.[119]
- Median time to first response for patients in Cohort C was just [redacted] months.[46] The responses elicited by talquetamab deepen over time; the median time to CR or better, VGPR or better was [redacted] ([redacted]) months and [redacted] ([redacted]) months, respectively.[46]
- Among responders, the median DoR in Cohort C was 17.5 months, with the DoR being substantially longer in patients who achieved the best responses.[119] For patients who achieved a ≥CR, the median DoR was [redacted] [95% CI, [redacted]], while the 25th percentile DoR was [redacted] months [95% CI, [redacted]]).[46]
- MRD negativity (at a threshold of 10^{-5} and 10^{-6}) was achieved in [redacted]% and [redacted]% of patients in Cohort C, respectively, indicating a clinically meaningful response to talquetamab.[46]

These responses translated to substantial survival benefits for patients who received talquetamab, with over 60% of patients receiving talquetamab still alive three years post-talquetamab initiation

- In total, [redacted]% of patients had experienced disease progression or death at the time of the September 2024 DCO.[46] The median PFS associated with talquetamab was 11.2 months (95% CI, 7.7, 14.6) and the 12-month PFS rate was [redacted]% (95% CI, [redacted], [redacted]).[46, 119]
- After a median follow-up of 31.2 months, [redacted]% of patients had died. The median OS was not yet reached (95% CI, NE, NE) in Cohort C, with OS rates at 12 months and 24 months of [redacted]% (95% CI, [redacted]) and [redacted]% (95% CI, [redacted]) respectively.[46, 119]
- The high 36-month OS rate of 60.8% (95% CI, 51.5, 68.8), suggests that the majority of patients are still alive after three years of talquetamab treatment, indicative of a substantial survival benefit for TCE RRMM patients.[119]

Efficacy results for Cohort C (0.8 mg/kg Q2W) from the September 2024 DCO of MonumenTAL-1 are provided in Sections 2.6.1–2.6.8 below. For completeness, the efficacy results for Cohort A (0.4 mg/kg SC QW) and Cohort B (Prior TCR) are presented in Appendix L.

Summary of MonumenTAL-1 DCOs

A summary of the DCOs from MonumenTAL-1 is provided in Table 15. As the trial matures, the ORR stabilises at around 70%, clearly demonstrating the high response rate sustained with talquetamab treatment.[119] There is also a general trend of increasing proportions of patients achieving a ≥CR, suggesting that the responses initiated by talquetamab deepen over time. As the most recent and [redacted], the September 2024 DCO is presented throughout this section.[46]

Table 15: MonumenTAL-1 efficacy outcomes over time (Cohort C [0.8 mg/kg Q2W])

Data cut	Median follow-up (months)	ORR, % (95% CI)	≥CR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
May 2022 (N=145)[151]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
September 2022 (N=145)[152]	8.6	73.1 ([redacted])	32.4 ([redacted])	NR	NR
January 2023 (N=145)[153]	12.7	71.7 ([redacted])	38.6 ([redacted])	14.2 (9.6, NE)	NE (20.1, NE)
January 2024 (N=154)[138]	23.4	69.5 ([redacted])	40.3 [redacted]	11.2 (8.4, 14.6)	[redacted]
September 2024 (N=154)[46, 119]	31.2	69.5 [redacted]	40.3 [redacted]	11.2 (7.7, 14.6)	NE (NE, NE)

Abbreviations: CI: confidence interval; CR: complete response; NE: not evaluable; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.
Source: J&J IM MonumenTAL-1 clinical study report (May 2022 DCO).[151] J&J IM MonumenTAL-1 clinical study report (September 2022 DCO).[154] Touzeau, *et al.* 2023.[153] Rasche *et al.* 2024.[138] J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

2.6.1 ORR (primary endpoint)

Disease control was highlighted as the most important attribute for a MM treatment by patients in a 2019 Myeloma UK study, and providing durable responses represent the first, crucial step towards this.[155] A further statement from Myeloma UK during the NICE appraisal for teclistamab also highlighted that 'Responding well to a treatment has a huge psychological impact on patients and their families'.[156]

The primary endpoint of MonumenTAL-1 was ORR, defined as the proportion of patients who achieved PR or better according to the IMWG criteria, as assessed by the IRC.[157] The primary endpoint was met in MonumenTAL-1 in Cohort C (0.8 mg/kg Q2W), with an overall response by IRC assessment experienced by the majority of patients. At a median follow-up of 31.2 months, talquetamab was associated with an ORR of 69.5% in Cohort C; N=154.[119] An overview of response rates and follow-up based on IRC assessment of patients in Cohort C is presented in Table 16 below.[46]

Treatment with talquetamab was associated with deep responses in those who achieved a response – ≥CR was reported in 40.3% of patients, with 31.2% of patients achieving a sCR and 9.1% of patients achieving a CR.[119] A further 18.8% of patients experienced a VGPR, resulting in a VGPR or better rate of 59.1% in Cohort C.[119] Time to response data are presented in Section 2.6.3.

Most responses occurred early and deepened over time. Results from previous DCOs of MonumenTAL-1 further demonstrate the deepening of responses with talquetamab treatment over time, with a consistent increase in the percentage of patients achieving a CR or better observed up to September 2024 ([redacted]%, 38.6%, 32.4%, and [redacted]% of patients achieving ≥CR in the January 2024, January 2023, September 2022, and May 2022 data cuts, respectively).[137, 151, 154]

Achieving a complete response is particularly important for patients with TCE RRMM, as having this level of response when they have cycled through the 3 main drug classes available provides a renewed sense of hope that they can expect their remission to last longer and that they are likely to live longer as a result. Prior to the approval of BCMA-targeted immunotherapies like teclistamab, very few patients with RRMM achieved this level of response. In the clinical trial of PomDex (the MM-003 trial), only 7% of patients achieved a ≥VGPR, highlighting how difficult it was to achieve with the previous standard of care treatments.[158] The many patients achieving a ≥CR with talquetamab will therefore feel a huge amount of relief and hope that their responses will be sustained, and translate into an improvement in their prognosis. As ORR and response depth is linked with overall survival (OS) in RRMM, the high ORR and complete response rate observed in patients receiving talquetamab would typically also correspond to sustained long-term survival outcomes observed in these patients.[159]

Table 16: Response rates of patients in Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Response rates, n (%)	Cohort C (0.8 mg/kg Q2W) [N=154]
ORR	107 (69.5%)
≥VGPR (sCR + CR + VGPR)	91 (59.1%)
≥CR (sCR + CR)	62 (40.3%)
sCR	48 (31.2%)
CR	14 (9.1%)
VGPR	29 (18.8%)
PR	16 (10.4%)
MR	[redacted]
SD	[redacted]
PD	[redacted]
Not evaluable	[redacted]

Abbreviations: CR: complete response; MR: minimal response; ORR: overall response rate; PD: progressed disease; PR: partial response; Q2W: biweekly; sCR: stringent complete response; SD: standard deviation: VGPR: very good partial response.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

2.6.2 *Duration of response (secondary endpoint)*

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. An overview of DoR in patients in Cohort C (0.8 mg/kg Q2W) is presented in Table 17.

Among responders (N=107), median DoR in Cohort C was 17.5 months (95% CI, 12.5 months, 25.1).[119] The Kaplan–Meier (KM) estimate of maintenance of response for at least 6 months was [redacted] (95% CI, [redacted]).[46] The probability of patients remaining in response at 12 months and 24 months was [redacted]% (95% CI, [redacted]) and [redacted]% (95% CI, [redacted]), respectively.[46] A KM curve showing the change in DoR over time, based on IRC assessment are provided in Figure 7 below.

For those who achieved ≥CR (N=62), DoR was improved in comparison to patients who achieved less complete responses, with numerically higher percentages of response at all timepoints at the time of the September 2024 DCO. The median DoR was [redacted] (95% CI, [redacted]), while the 25th percentile DoR for patients who achieved a CR or better was [redacted] months (95% CI, [redacted]). In comparison with all responders, where the 25th percentile DoR was [redacted] months (95% CI, [redacted]). The extended DoR for patients who achieved ≥CR demonstrates the long-term benefit of talquetamab in those who achieve the best responses to treatment and also demonstrates that the DoR is substantially longer for patients achieving a CR, compared with those who achieve a VGPR or PR.

Therefore, with a combination of a high ORR and DoR, talquetamab is anticipated to provide a prolonged treatment benefit to the patients who respond.

Table 17: Duration of response in patients in Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Duration of response	Total CR or better population [N=62]	Total PR or better population (All responders) [N=107]
Number of events, n (%)	[redacted]	[redacted]
Number of events censored, n (%)	[redacted]	[redacted]
6-month event-free, % (95% CI)	[redacted]	[redacted]
9-month event-free, % (95% CI)	[redacted]	[redacted]
12-month event-free, % (95% CI)	[redacted]	[redacted]
18-month event-free, % (95% CI)	[redacted]	[redacted]
24-month event-free, % (95% CI)	[redacted]	[redacted]
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	17.5 (12.5, 25.1)
75% percentile (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CR: complete response; NE: not estimable; NR: not reported; PR: partial response; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

Figure 7: KM plot for DoR based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Footnote: The 'Total RP2D' represents the overall Cohort C considered in this submission. This consists of a combination of patients from 'Phase 1 RP2D' and 'Phase 2 Cohort C' groups.
Abbreviations: DoR: duration of response; IRC: independent review committee; RP2D: recommended Phase II dose; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.6.3 Time to response (secondary endpoint)

TCE RRMM patients receiving talquetamab demonstrated a short median (range) time to first response of [redacted] months ([redacted]), in Cohort C (0.8 mg/kg Q2W).[46] This response time illustrates the rapid onset of response triggered by the innovative mechanism of action of talquetamab. As presented in Table 18, the median (range) time to best response in Cohort C was [redacted] months ([redacted]), illustrating that patients' responses develop over time.[46]

When assessing time to response by depth of response, the median time to CR or better, VGPR or better was [redacted] ([redacted]) months and [redacted] ([redacted]) months, respectively, highlighting that the deepest responses develop over time.[46] A summary of time to response by depth of response for patients in Cohort C in MonumenTAL-1 is provided in Table 18.

Table 18: Time to response by depth of response; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

Time to response	Responders in Cohort C (0.8 mg/kg Q2W)
Time to first response, months	[N=107]
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Time to best response, months	[N=107]
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]

Time to VGPR or better, months	[N=91]
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Time to CR or better, months	[N=62]
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]

Abbreviations: CR: complete response; PR: partial response; SD: standard deviation; VGPR: very good partial response.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.6.4 MRD negativity rate (secondary endpoint)

MRD was defined as the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} and 10^{-6} at any timepoint after initial dose of talquetamab and before disease progression or starting subsequent therapy. MRD is a strong prognostic marker for survival across the MM disease spectrum, making it a valuable clinical endpoint when assessing the efficacy of emerging therapeutics.[46, 160]

A summary of MRD negativity rate at 10^{-5} and 10^{-6} in the bone marrow is presented in Table 19. Negativity for MRD (at a threshold of 10^{-5} and 10^{-6}) was achieved in [redacted] and [redacted] of patients in Cohort C (0.8 mg/kg Q2W), respectively. These patients had no detectable cancer cells at a highly sensitive level, indicating a clinically meaningful response to talquetamab, which as outlined above is associated with the response depth (as presented in Section 2.6.1) and subsequently will result in improvements in long-term survival.

Table 19: Overall MRD negativity rate at 10^{-5} and 10^{-6} in the bone marrow; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

MRD negativity rate	Cohort C (0.8 mg/kg Q2W) [N=154]	
Threshold of 10^{-5}		**95% CI**
Proportion of patients, n (%)	[redacted]	[redacted]
Threshold of 10^{-6}		**95% CI**
Proportion of patients, n (%)	[redacted]	[redacted]

Footnotes: MRD status based on next generation sequencing (NGS) results.
Abbreviations: CI: confidence interval; MRD: minimal residual disease; NGS: next generation sequencing; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.6.5 Progression-free survival (secondary endpoint)

Due to the increased symptom burden experienced by patients as the disease progresses, prolonging the time patients are in a progression-free state is vital in preventing the decrement in HRQoL following disease progression.[86] Results from the 2019 Myeloma UK study suggested that patients do value '*longer remission/treatment-free periods*', which underscores the importance of PFS as an outcome.[161]

After a median follow up of 31.2 months, in Cohort C (0.8 mg/kg Q2W) the median PFS was 11.2 months (95% CI, 7.7, 14.6).[119] The estimated PFS rate at 12 months and 24 months was [redacted]% (95% CI, [redacted]) and [redacted]% (95% CI, [redacted]), respectively.[46] A summary of PFS results in Cohort C is provided in Table 20 and a KM plot for PFS is presented in Figure 8. Talquetamab would therefore provide patients with a sustained period of remission, delaying the psychological impact associated with relapsing, providing them with precious time to remain healthy and spend with their loved ones.

Table 20: Progression-free survival based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

PFS Results	Cohort C (0.8 mg/kg Q2W) [N=154]
Number of events, n (%)	[redacted]
Number of events censored, n (%)	[redacted]
6-month PFS rate, % (95% CI)	[redacted]
9-month PFS rate, % (95% CI)	[redacted]
12-month PFS rate, % (95% CI)	[redacted]
18-month PFS rate, % (95% CI)	[redacted]
24-month PFS rate, % (95% CI)	[redacted]
Median KM estimate, months (95% CI)	
25% percentile (95% CI)	[redacted]
Median (95% CI)	11.2 (7.7, 14.6)
75% percentile (95% CI)	[redacted]

Abbreviations: CI: confidence interval; IRC: independent review committee; PFS: progression-free survival; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

Figure 8: KM plot for PFS based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Footnotes: The 'Total RP2D' represents the overall Cohort C considered in this submission. This consists of a combination of patients from 'Phase 1 RP2D' and 'Phase 2 Cohort C' groups.

Abbreviations: IRC: independent review committee; KM: Kaplan Meier; PFS: progression-free survival; Q2W: biweekly; RP2D: recommended Phase II dose.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.6.6 Time to next treatment

TTNT was defined as the time to subsequent treatment (excluding radiotherapy) or death (including deaths due to AE). Note that TTNT represents a distinct endpoint to time to subsequent anti-myeloma therapy defined in the MonumenTAL-1 CSR, which includes radiotherapy and does not include deaths due to AEs.

The median TTNT in Cohort C was [redacted] months (95% CI, [redacted]). In total, a time to next treatment event occurred in [redacted] patients ([redacted]%). A KM curve of TTNT for patients in Cohort C is presented in Figure 9.

Figure 9. KM plot for time to next treatment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Abbreviations: CI: confidence interval; KM: Kaplan-Meier; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.6.7 Overall survival (secondary endpoint)

Myeloma patients and their carers place a very high value on treatments that prolong their life.[162] RRMM is currently a predominantly incurable disease, and therefore prolonging patients' lives so they can spend more time with their loved ones is of the upmost importance. Patients may also view gains in survival as a bridge to further treatments becoming available in the future. As such, improving patients' prognoses could allow them to benefit from future advancements in their treatment, underlining the importance of OS as an outcome.

At the time of the September 2024 DCO, [redacted] OS events had occurred in Cohort C (0.8 mg/kg Q2W), with median OS not reached (NE [95% CI, NE, NE[redacted]).[46, 119] The 25th percentile OS estimate was [redacted][46] A summary of OS is provided in Table 21. A KM plot illustrating the OS with talquetamab in Cohort C (0.8 mg/kg Q2W) of MonumenTAL-1 is depicted in Figure 10 (split by patients in phase 1 and 2) and Figure 11 (overall Cohort C, total RP2D).

Table 21: Overall survival; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut)

Overall Survival	Cohort C (0.8 mg/kg Q2W) [N=154]
Number of events, n (%)	[redacted]
Number of censored (%)	[redacted]
6-month OS rate, % (95% CI)	[redacted]
9-month OS rate, % (95% CI)	[redacted]
12-month OS rate, % (95% CI)	[redacted]
24-month OS rate, % (95% CI)	[redacted]
36-month OS rate, % (95% CI)	60.8 (51.5, 68.8)
Median KM estimate, months (95% CI)	
25% percentile	[redacted]
Median	NE (NE, NE)
75% percentile	[redacted]

Abbreviations: CI: confidence interval; KM: Kaplan Meier; OS: overall survival; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

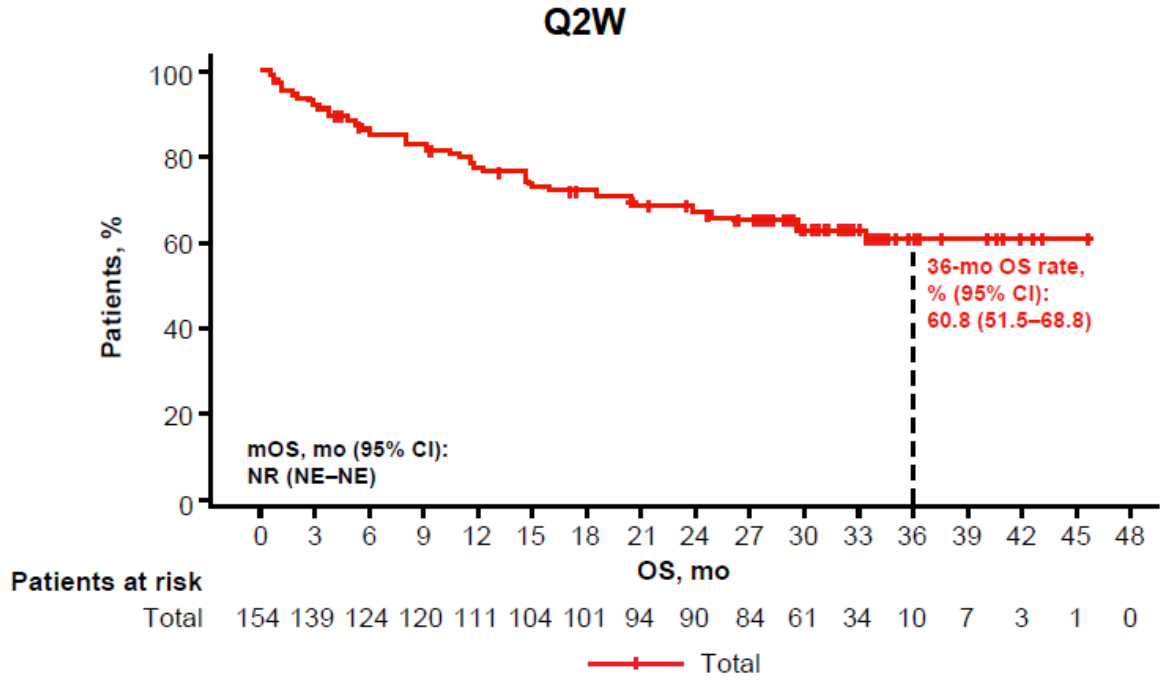
The OS rates at 12 months and 24 months were [redacted]% (95% CI, [redacted]) and [redacted]% (95% CI, [redacted]), respectively.[46] As shown in Table 21, the high 36-month OS rate of 60.8%, suggests that most patients enrolled in Cohort C are still alive after three years of talquetamab treatment, clearly demonstrating the survival benefits talquetamab could provide to TCE RRMM patients.[119] This survival is linked to high response rates and depth as well as the MRD-negativity rate associated with talquetamab, that have been demonstrated throughout Section 2.6.

It is acknowledged that owing to the international nature of the trial, some patients in MonumenTAL-1 received subsequent treatments that are not relevant to UK clinical practice, however, analyses presented in Section 2.10.6 demonstrate that these had a minimal impact on the OS observed in MonumenTAL-1.

Figure 10: KM plot for overall survival; Cohort C (0.8 mg/kg Q2W), split by phase (September 2024 data cut)

Footnotes: The 'Total RP2D' represents the overall Cohort C considered in this submission. This consists of a combination of patients from 'Phase 1 RP2D' and 'Phase 2 Cohort C' groups.
Abbreviations: KM: Kaplan Meier; Q2W: biweekly; RP2D: recommended phase II dose.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

Figure 11: KM plot for overall survival; Cohort C (0.8 mg/kg Q2W), total RP2D from Rasche, *et al* 2025 (September 2024 data cut)



Abbreviations: CI: confidence interval; KM: Kaplan Meier; mo: months; NE: not estimable; NR: not reported; OS: overall survival; Q2W: biweekly.
Source: Rasche *et al.* 2025.[119]

2.6.8 Patient-reported outcomes

Please note that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline and therefore not presented in this section. It will be provided as an addendum when possible.

2.7 Subsequent treatments used in the relevant studies

In total, [redacted]% (N=[redacted]) of all patients in Cohort C (N=154) survived progression and started at least one subsequent therapy on or after progression date. Of the patients receiving subsequent therapy (N=[redacted]), the most commonly received subsequent treatments were carfilzomib plus chemotherapy ([redacted]%) and teclistamab ([redacted]%).[46]

A summary of the subsequent therapy regimens received by patients in Cohort C (0.8 mg/kg Q2W) in the MonumenTAL-1 trial as of the September 2024 DCO are presented in Table 22. For completeness, a full list of subsequent therapies received by patients in Cohort C can be found in Appendix L. Relevant information on the subsequent treatment duration of patients is provided in Section 3.5.4.

Adjusting for non-relevant subsequent treatments

Due to the international nature of the MonumenTAL-1 trial, some patients received some subsequent treatments that are not currently available in UK clinical practice. As such, Table 22 distinguishes between the UK-relevant and non-UK relevant treatments, with key points summarised below:

- The most commonly received UK-relevant subsequent treatments in Cohort C were teclistamab ([redacted]%) and cyclophosphamide-based regimens ([redacted]%).
- Non-relevant UK subsequent treatments mostly included carfilzomib or daratumumab. Carfilzomib is only recommended for use within the NHS at second- and third-line and, therefore, it is unlikely to be a subsequent therapy for TCE RRMM patients in the UK. Daratumumab was excluded as subsequent therapy as, based on the current UK RRMM treatment pathway, most patients will have received daratumumab to become TCE, with many patients also refractory to daratumumab prior to receiving talquetamab.
- A small proportion of patients in Cohort C received non-UK subsequent treatment with unspecified CAR-T cell therapy ([redacted]%), ciltacabtagene autoleucel ([redacted]%) or idecabtagene vicleucel ([redacted]%). It is acknowledged that for this small proportion of patients, OS outcomes may be slightly different to those expected in UK clinical practice.[163]

Consequently, to improve the relevance of the clinical effectiveness data for talquetamab, the OS data from MonumenTAL-1 were adjusted using the two-stage adjustment process outlined in NICE TSD16 in order to censor the effects of subsequent treatments that are not routinely available in UK clinical practice (as detailed in Section 2.10.6).[164] Full details of the two-stage adjustment are detailed in Section 2.10.4. Health economic experts consulted by the Company validated that the two-stage subsequent treatment adjustment to remove non-UK relevant treatments is appropriate, and valued the consistency with the approach accepted by NICE in the appraisal of teclistamab [TA1015].[76]

The distribution of subsequent treatments used in Cohort C following the OS adjustment is presented in Table 22. The results were validated by clinical experts as being broadly reflective of UK clinical practice, with the exception of the omission of elranatamab, which would otherwise be used in UK clinical practice but was intentionally removed as it is currently funded via the CDF and therefore cannot be considered as routine clinical practice in this submission.[96]

Table 22: Summary of subsequent therapies received by patients in MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

Patients receiving subsequent therapies, %	Unadjusted Cohort C (0.8 mg/kg Q2W) [N=80]	UK-specific adjusted[f] Cohort C (0.8 mg/kg Q2W)
UK-relevant subsequent therapy		
Bendamustine-based regimens	[redacted]	[redacted]
Bortezomib plus chemotherapy	[redacted]	[redacted]
Cisplatin plus chemotherapy	[redacted]	[redacted]
Cyclophosphamide-based regimens	[redacted]	[redacted]
Pomalidomide-based regimens	[redacted]	[redacted]
Dexamethasone monotherapy	[redacted]	[redacted]
Melphalan-based regimens	[redacted]	[redacted]
Lenalidomide monotherapy	[redacted]	[redacted]
Methylprednisolone monotherapy	[redacted]	[redacted]
Selinexor monotherapy	[redacted]	[redacted]
Teclistamab monotherapy	[redacted]	[redacted]
Non-UK relevant subsequent treatments[a]		
Belantamab-based regimens	[redacted]	
Bendamustine-based regimens[b]	[redacted]	
Bortezomib plus chemotherapy[c]	[redacted]	
CAR-T cell therapies	[redacted]	
Carfilzomib plus chemotherapy	[redacted]	
Cevostamab plus chemotherapy	[redacted]	
Ciltacabtagene autoleucel-based regimens	[redacted]	
Cyclophosphamide-based regimens[d]	[redacted]	
Daratumumab-based regimens	[redacted]	
Dexamethasone-based regimens[e]	[redacted]	
Idecabtagene vicleucel	[redacted]	
Investigational antineoplastic drugs	[redacted]	
Linvoseltamab-based regimens	[redacted]	
Venetoclax	[redacted]	

Footnotes: [a] This summary of non-UK relevant subsequent treatments only presents treatments received by >1 patient. A table of the full subsequent treatment distribution in MonumenTAL-1 is presented in Appendix L. Note that the total subsequent treatment percentage for non-UK relevant subsequent treatments does not total 100% as a patient could have received multiple subsequent treatments.
[b] Non-UK relevant bendamustine-based regimens included bendamustine hydrochloride ciltacabtagene autoleucel cyclophosphamide dexamethasone fludarabine phosphate lenalidomide, bendamustine bortezomib dexamethasone, and bendamustine CAR-T NOS cyclophosphamide dexamethasone fludarabine. [46]
[c] Non-UK relevant bortezomib plus chemotherapy regimens included bortezomib cisplatin cyclophosphamide daratumumab doxorubicin etoposide, bortezomib cyclophosphamide dexamethasone, bortezomib cyclophosphamide dexamethasone pomalidomide, bortezomib dexamethasone pomalidomide and bortezomib

linvoseltamab.[165]
[d] Non-UK relevant cyclophosphamide-based regimens included cyclophosphamide daratumumab thalidomide and cyclophosphamide fludarabine idecabtagene vicleucel.[165]
[e] Non-UK relevant dexamethasone-based regimens included dexamethasone elotuzumab pomalidomide, dexamethasone isatuximab pomalidomide, dexamethasone lenalidomide TNB 383B, dexamethasone pomalidomide selinexor, dexamethasone pomalidomide TNB 383B.[165]
[f] Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%
Abbreviations: Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.8 Subgroup analysis

The NICE final scope specified that, if the evidence allows, subgroups by prior T-cell redirection therapy and prior lines of therapy will be considered.

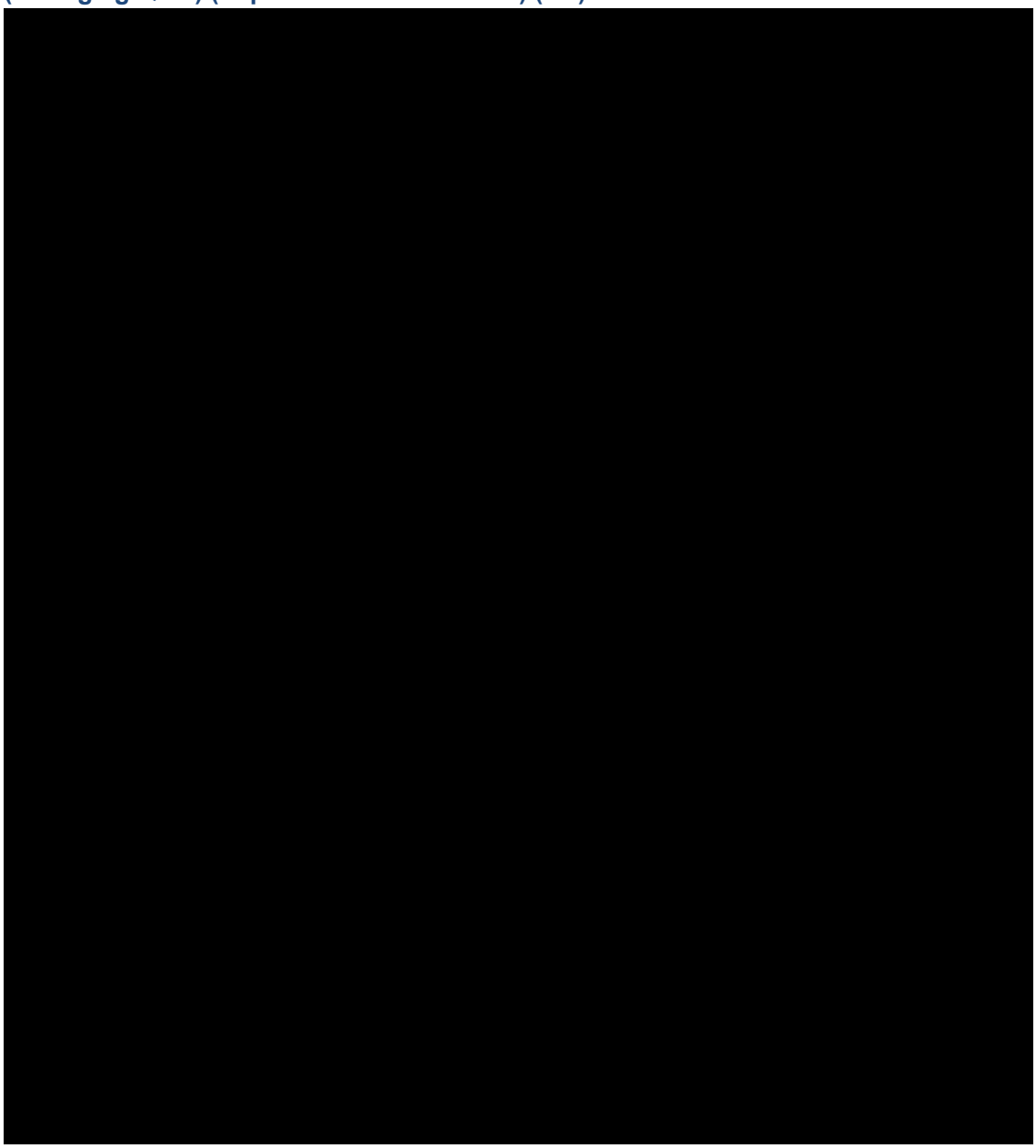
As detailed in Section 1.1, the current evidence does not permit consideration of subgroups based on their prior T cell redirection therapy. This is because the (1) The population of TCR-exposed patients in UK clinical practice is currently very small (consistent with the orphan designation status of talquetamab in this indication), due to the recency of the recommendations for both teclistamab (November 2024) and elranatamab (December 2024, via the CDF).[3, 7, 8], and (2) as previously outlined in MonumenTAL-1, Cohort B exclusively included patients who had previously received BCMA-targeting TCR therapies. The vast majority of these patients (73.1%) had prior exposure to CAR-T therapies, reflecting the international nature of MonumenTAL-1.[117] Since CAR-T therapies are not currently available to NHS patients with TCE RRMM, this cohort presents limitations for decision making compared to the results from Cohort C. As such, subgroup analyses based on Cohort B have not been presented.

However, subgroup analyses of ORR in MonumenTAL-1 were performed based on baseline disease characteristics, baseline demographic characteristics and number of lines of prior therapies, with the results presented in Figure 12 to Figure 14 below. At a median follow-up of 31.2 months, in the September 2024 DCO, subgroup analyses demonstrate that the response rates associated with talquetamab were highly consistent across patient subgroups stratified by a range of baseline and disease characteristics.[117] The use of prior therapy (i.e., number of prior LOT and refractory status) was not associated with any meaningful difference in ORR (Figure 13, rows 1-6).

The only statistically significant differences in ORR between patient subgroups and the overall population were observed for patients with baseline R-ISS stage III and extramedullary plasmocytomas.[46] The ORR with talquetamab was lower for patients with R-ISS stage III and ≥1 extramedullary plasmacytoma, compared to the overall patient population in MonumenTAL-1, as these characteristics are indicative of patients with more severe disease that is harder to treat. Meanwhile, patients with no extramedullary plasmacytoma had a higher ORR ([redacted]%) with talquetamab than the overall patient population in Cohort C. It is important to note that both R-ISS and extramedullary plasmacytomas are well established in the literature as important prognostic factors for patients with MM, and as subsequently detailed in Section 2.10, these variables were identified by clinical experts as 'priority variables' for patients with MM.[166] Therefore, it is entirely expected that treatment with talquetamab resulted in a lower ORR in these patient populations ([redacted]% and [redacted]%, respectively). Given that these patient populations have a high risk of disease progression, the ORRs elicited by talquetamab are still relatively high, and the primary endpoint was still met (ORR of greater than 30%).[46]

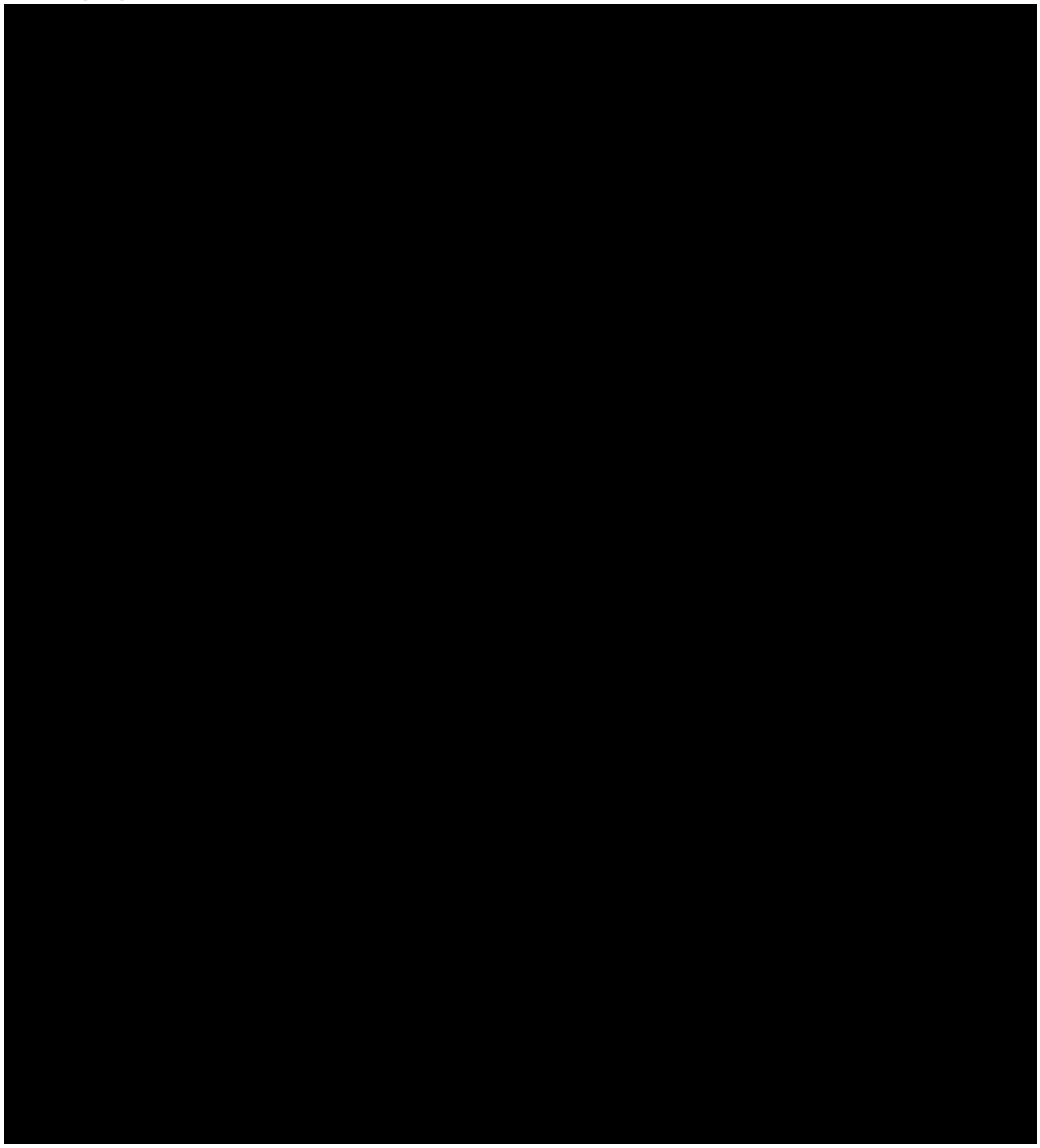
Overall, the subgroup analyses clearly highlight the consistency of the high responses that talquetamab provides across the majority of subgroups; supporting the absence of subgroup effect in the patient population of interest.

Figure 12: Forest plot of subgroup analyses for ORR based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut) (1/3)



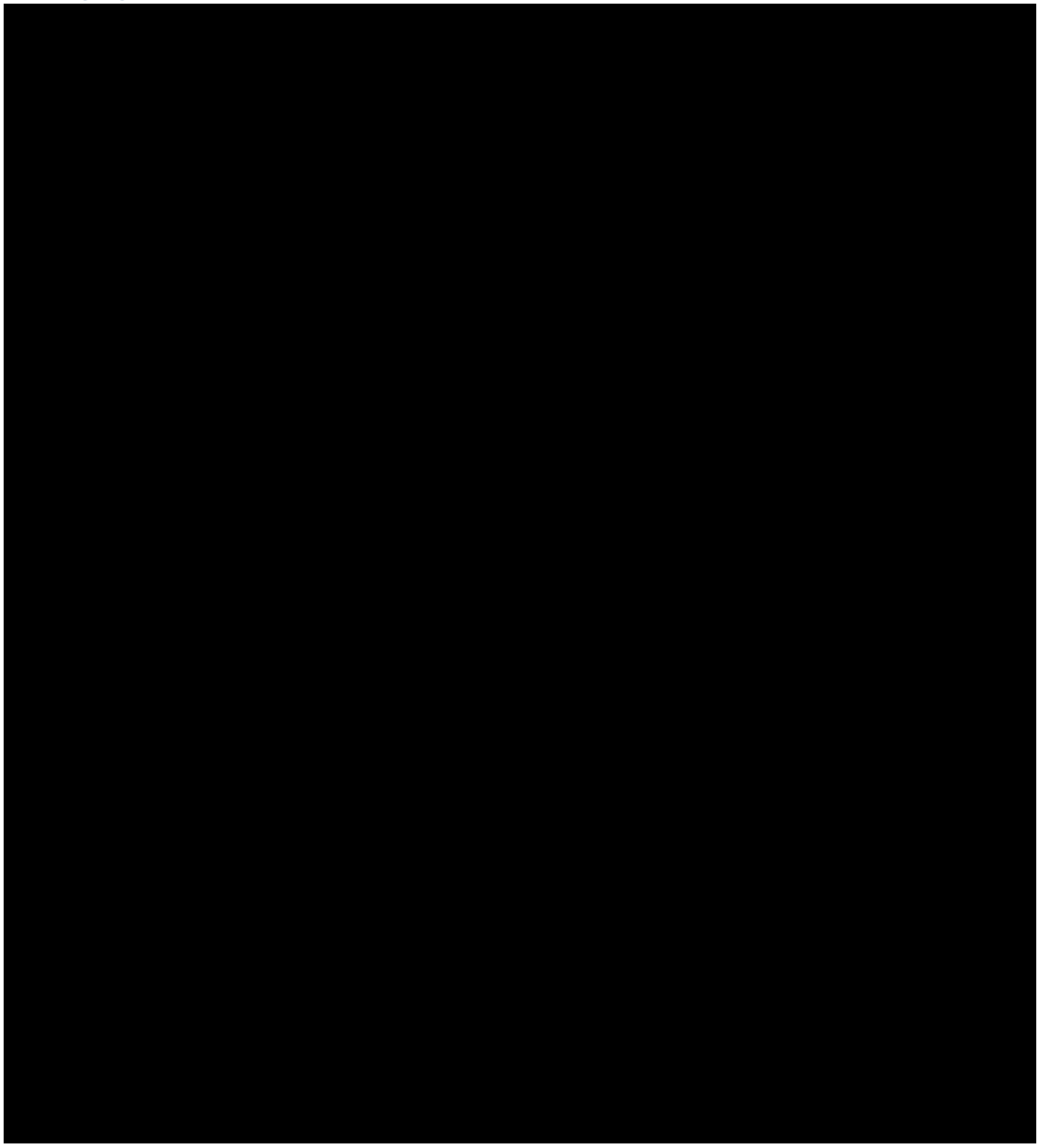
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperativity Group Oncology score; IRC: independent review committee; ORR: overall response rate; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

Figure 13: Forest plot of subgroup analyses for ORR based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut) (2/3)



Abbreviations: CI: confidence interval; IgG: immunoglobulin class G; IMiD: immunomodulatory drug; IRC: independent review committee; ISS: international staging system; ORR: overall response rate; PI: proteasome inhibitor; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

Figure 14: Forest plot of subgroup analyses for ORR based on IRC assessment; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut) (3/3)



Abbreviations: ADC: antibody-drug conjugate; CI: confidence interval; GPRC5D: G protein coupled receptor class 5D; ORR: overall response rate; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.9 Meta-analysis

As MonumenTAL-1 is the only trial for talquetamab in the population of relevance to this indication and due to the single-arm nature of the trial, meta-analysis was not possible.

2.10 Indirect and mixed treatment comparisons

The data source informing the clinical effectiveness of talquetamab versus teclistamab is anchored on high-grade indirect evidence, i.e. a robust trial-vs-trial ITC leveraging IPD from the MonumenTAL-1 and MajesTEC-1 trials.

- In the absence of direct trial evidence comparing the effectiveness of talquetamab to teclistamab, ITCs were conducted between MonumenTAL-1 and MajesTEC-1; IPD were available from both trials as the Company was the sponsor for those.[45, 46]
- In line with NICE TSD17, the MajesTEC-1 cohort was reweighted to mimic MonumenTAL-1.[120] All 17 identified key prognostic variables were adjusted using an IPTW ATT-weighting approach, where the MajesTEC-1 cohort was re-weighted to align with the baseline characteristics in MonumenTAL-1. This approach was considered appropriate as MonumenTAL-1 was assumed to be broadly generalisable to patients who would receive talquetamab in UK clinical practice.
- Prior to adjustment, 15 out of the 17 prognostic variables had standardised mean differences (SMDs) within a ±0.2 threshold. This indicates a high degree of overlap between the two trials prior to adjustment and negates the need for trimming or truncation prior to IPTW adjustment
- Following adjustment, the two trials were well balanced with respect to all 17 prognostic variables, with an SMD <0.2 in all cases.
- Overall, HTA experts commented that the ITC analyses presented were methodologically robust and clinical experts indicated that the patient population in MonumenTAL-1 is generalisable to UK clinical practice, meaning that the ITC results would be externally valid to the UK population of patients with TCE RRMM.

The results of the ITC demonstrated that talquetamab is expected to elicit a greater overall response rate, and comparable response depth compared to teclistamab

- Following ATT adjustment, patients receiving talquetamab had a significantly higher likelihood of experiencing an overall response (RR: [redacted] [95% CI: [redacted]]; p=[redacted]) compared to patients receiving teclistamab. As such, in spite of patients in MonumenTAL-1 having slightly more advanced disease, these results suggest that there is a greater breadth of patients positively responding to talquetamab treatment compared to teclistamab.
- Treatment with talquetamab resulted in a similar likelihood of achieving a complete response when compared to teclistamab (RR: [redacted] [95% CI:[redacted], p=[redacted]), suggesting that both induce deep responses in TCE RRMM patients.
    - Similarly, the DoR was also comparable for patients receiving talquetamab versus teclistamab (HR: [redacted] [95% CI: [redacted] p=[redacted]), suggesting that both elicit equally deep and durable responses.

The results of the ITC established that talquetamab elicits statistically significant and clinically meaningful improvements in OS versus teclistamab, with a [redacted]% reduction in the risk of death over time

- Patients receiving talquetamab had comparable PFS to patients receiving teclistamab (HR: [redacted] [95% CI, [redacted] p=[redacted]).
- To improve the relevance of the clinical effectiveness data for talquetamab, a two-stage subsequent treatment adjustment was performed to remove the effects of non-routine subsequent treatments in UK clinical practice. The ITC results following IPTW ATT-weighting and two-stage subsequent treatment demonstrated that talquetamab was associated with a statistically significant improvement in OS when compared to

teclistamab, with a [redacted] reduction in the risk of death (HR: [redacted] [95% CI: [redacted]], p[redacted]).
    - This OS benefit for talquetamab over teclistamab was maintained across the scenario analyses which explored differences in subsequent treatment distributions in MonumenTAL-1 and MajesTEC-1. In these scenarios, the effect of subsequent treatment with BsAbs after teclistamab (i.e., talquetamab) and after talquetamab (i.e., teclistamab) was completely removed (All-out scenario: HR: [redacted] [95% CI, [redacted] p=[redacted]) or alternatively, was included (All-in scenario: HR: [redacted] [95% CI, [redacted]]; p=[redacted]).
    - These results were highly consistent with the base case ITC results and therefore, demonstrated that the OS benefit observed with talquetamab cannot be attributed to differences in the subsequent treatments received in MonumenTAL-1 and MajesTEC-1.
- The ITC results remained consistent across an extensive range of sensitivity analyses including alternative weighting approaches, multivariate regression and propensity score matching. In these scenarios, OS HRs were highly consistent across analyses, thus strongly supporting the significant survival benefit that talquetamab provides.
- Additional sensitivity analyses using the combined Cohort A+C (weighted 10:90 as per clinical expert feedback) for talquetamab compared with teclistamab, were consistent with the main ITC (HR: [redacted] [95% CI [redacted]], p<[redacted]), demonstrating the robustness of the results around the OS benefit.

Conclusions

- The significant OS benefit of talquetamab consistently demonstrated over teclistamab across the various sensitivity analyses conducted in Section 2.10.6. [redacted]
    - As a BCMA-targeting BsAb, teclistamab is known to result in disruptions to patients' humoral immunity.[32-36, 38, 39] Meanwhile, as talquetamab targets GPRC5D specifically expressed by MM cells, this may allow patients to maintain better long-term immune function compared to BCMA-targeting BsAbs.[42, 167]
    - Patients receiving talquetamab have a lower rate of life-threatening infections and infection-related mortality than those receiving teclistamab, [redacted]

SLR

As reported in Section 2.1, the clinical SLR identified 87 studies in RRMM reporting on 27 unique studies. The full details of the methodology and results of the clinical SLR are reported in Appendix B. No studies were identified directly comparing talquetamab with teclistamab, the relevant comparator in this submission.

The clinical SLR identified two studies of teclistamab in the patient population of interest to this submission, which were past the recruitment stage at the time of the SLR, the MajesTEC-1 trial (NCT04557098) and Ishida 2024 (NCT04696809).[124] [168] Of these studies, MajesTEC-1 is larger and included an international cohort of patients, while Ishida 2024 is only focussed on Japan.[124] [168] Additionally, MajesTEC-1 was the primary clinical evidence source informing the NICE appraisal for teclistamab in the treatment of TCE RRMM [TA1015].[3] Therefore the MajesTEC-1 trial was considered to represent the most appropriate data source for teclistamab to inform the comparative efficacy evidence in this submission. As the Sponsor of both MajesTEC-1 and

MonumenTAL-1, the Company had access to individual patient data (IPD) of both trials, which is a key strength to generate high-grade indirect evidence to inform decision making for this submission.

MajesTEC-1 study

MajesTEC-1 is a Phase I/II, open-label, single-arm, international, multicentre study investigating the safety and efficacy of teclistamab as a monotherapy in adult patients with TCE RRMM.[40] This study served as the registrational evidence supporting the license application for teclistamab in adult patients with TCE RRMM who had demonstrated disease progression on their last therapy.[143, 169] The primary endpoint in the MajesTEC-1 trial was ORR, with key secondary endpoints including OS and PFS.[40] The cohort of patients who received the RP2D dose of teclistamab, referred to as the "All Treated Analysis Set (N=165)", in the MajesTEC-1 trial informed the comparative efficacy evidence of teclistamab versus talquetamab. This was based on the final prespecified DCO of August 2023, with a median follow-up of 30.4 months, which also informed TA1015.[3]

A summary of the study is presented in Table 23 and full details, including the methods, baseline characteristics and study results, are presented in Appendix B. The modified Downs and Black tool providing a quality assessment of the MajesTEC-1 trial has also been provided in Appendix B. The risk of bias was estimated to be low, indicating that the robustness of MajesTEC-1 as a source of evidence. This assessment is further supported by UK clinical experts who deemed the MajesTEC-1 trial to be generalisable to UK clinical practice and the Committee accepted the trial as an appropriate source of clinical-effectiveness evidence for teclistamab in TCE RRMM patients.[3]

Table 23: Summary of the methodology of MajesTEC-1

Trial name	MajesTEC-1
Location	**Phase I:** France, Netherlands, Spain, Sweden, US **Phase II:** UK, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, US, Canada, China
Trial design	A Phase I/II, first-in-human, open-label, multicentre study of teclistamab monotherapy in patients with RRMM
Patient population of relevance to ITC	**All Treated Analysis Set (N=165):** Phase II (Cohort A; N=125): Patients with RRMM who received ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb (TCE) Phase I (RP2D cohort; N=40): Patients receiving the RP2D in Phase I (Part 2) who received ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb (TCE)
Key Inclusion/exclusion criteria (for the All Treated Analysis Set)	**Inclusion criteria:** • ≥18 years of age • Documented diagnosis of MM according to IMWG diagnostic criteria[118] • Eastern Cooperative Oncology Group (ECOG) performance score (PS) score of 0 or 1 • Previously received at least three lines of therapy (including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody (anti-CD38 mAb) and have had progressive, measurable disease at screening **Exclusion criteria:** • Previous treatment with a BCMA-targeting therapy
Method of study drug administration	**Phase I only**
	Part 1 (dose escalation) dosing: • Teclistamab IV: 0.0003 to 0.0192 mg/kg Q2W and 0.0192 to 0.72 mg/kg Q1W • Teclistamab SC: 0.08 to 1.5 mg/kg weekly Part 2 (dose expansion) dosing: • Treatment doses of 0.72 mg/kg teclistamab IV weekly and 1.5 mg/kg teclistamab SC weekly were expanded • Patients received a 1.5 mg/kg SC weekly treatment dose of teclistamab, with the first treatment dose proceeded by single SC step-up doses of 0.06 and 0.3 mg/kg on Days 3 and 5
	Phase II only
	Teclistamab SC Q1W at a dose of 1.5 mg/kg, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg Q1W on Days 3 and 5
	Phase I and II

	• Patients received teclistamab in all Phases until disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study (defined as two years after the last patient's first dose) • Patients in the MajesTEC-1 All Treated Analysis Set were allowed to switch to Q2W treatment upon meeting the following response criteria: • Phase I patients were required to have a confirmed PR or better and have received a minimum of 4-cycles of treatment. • Phase II patients were required to have a response of CR/sCR for a minimum of 6 months • As per the protocol amendment on the 5th of July 2021, patients were permitted to switch to Q4W dosing with Sponsor approval (Phase I), or if they were in response of CR or better at Cycle 12 Day 1 or later and had been receiving Q2W dosing for a minimum of 6 months (Phase II) • Patients were permitted to switch to less frequent dosing to manage toxicity per investigator discretion
Primary outcomes	**Phase I:** • AEs, SAEs and laboratory values (Part 2 only) **Phase II:** • ORR, as assessed by the independent review committee (IRC) based on International Myeloma Working Group (IMWG) criteria[118]
Secondary and exploratory outcomes	**Secondary outcomes:** • DoR • OS • PFS • sCR • ≥CR • PR • ≥VGPR • MRD negativity rate • AEs • EORTC QLQ-C30 scores • EQ-5D-5L VAS scores **Exploratory outcomes:** • Time to next treatment (TTNT) • Relationships between pharmacokinetics, pharmacodynamics, adverse event profile, and clinical activity of teclistamab • Predictive biomarkers of response or resistance to teclistamab

	• Pharmacodynamic markers • Immunoregulatory activity of teclistamab • MRD negativity rate for patients in standard-risk and high-risk molecular subgroups
Duration of study and follow-up	The first patient in the study was treated on 16th May 2017 and at the final DCO (August 2023), the median duration of follow-up was 30.4 months (range [redacted]) for the All Treated Analysis Set.

Abbreviations: AE: adverse event; CR: complete response; DCO: data cut-off; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; Ig: immunoglobin; IMiD: immunomodulatory agent; IMWG: International Myeloma Working Group; IV: intravenous; ISS: International Staging System; MM: multiple myeloma; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PI: proteasome inhibitor; PR: partial response; PS: performance score; RRMM: relapsed/refractory multiple myeloma; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; TTNT: time to next treatment; UK: United Kingdom; US: United States; VGPR: very good partial response.
Source: J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO);[40] MajesTEC-1 Clinical Protocol.[141]

Data availability

MajesTEC-1 phase II contained three cohorts, A, B and C. Cohort A contained patients with RRMM who received ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb (TCE). At the time of the final prespecified DCO (August 2023) of MajesTEC-1, Cohort B, containing heavily pre-treated patients considered penta-drug refractory, was not open for enrolment. Cohort C included patients who had previously received an anti-BCMA (including CAR-T therapy) treatment. Teclistamab is currently the only routinely recommended anti-BCMA treatment in UK clinical practice.[3] Therefore, in current UK clinical practice, patients eligible for teclistamab are unlikely to have received any previous anti-BCMA treatment, including CAR-T therapies. As such, patients in Cohort C are not reflective of any patient groups in the UK and were not considered relevant to inform the comparative efficacy data for teclistamab.

As noted above, the All Treated Analysis Set (N=165) in MajesTEC-1 (i.e., patients in Phase I receiving the RP2D dose of teclistamab (N=40) and patients in Cohort A (N=125) in Phase II of the trial) informed the clinical efficacy of teclistamab in the ITC.

The key endpoints informing the submission for talquetamab from MonumenTAL-1 were also captured in MajesTEC-1. Therefore, it was deemed appropriate to indirectly compare outcomes in MonumenTAL-1 versus MajesTEC-1. **As the Sponsor for both trials with full access to individual patient data (IPD), a thorough range of ITCs was robustly explored, as described below.**

2.10.1 Analysis methods

ITC methodology

Naïve comparisons of non-randomised data are typically biased due to confounding arising from imbalances between study populations for prognostic factors of interest. In these situations, multivariable regression and propensity score (PS) analyses – both of which are established methods recognised by NICE – are routinely used to estimate relative treatment effects while adjusting for observed differences between populations of interest.[120]

Regression refers to a class of methods in which an endpoint of interest (i.e., dependent variable) is related to a treatment indicator and one or more covariates. In contrast, PS-based methods involve weighting, matching or stratifying based on an estimated PS. PSs represent the conditional probability that a patient is assigned to an intervention based on their baseline observed covariates.[170, 171] These probabilities are derived using generalised linear models for binary outcomes (typically a logit or a probit model).

Although matching methods (e.g., nearest neighbour matching) are among the most commonly used PS methods, weighting (i.e., inverse probability of treatment weighting [IPTW]) is generally considered more efficient, since it leverages information from all patients rather than a limited subset of patients with available data and similar PSs. IPTW utilises the propensity score to derive weights for each individual so that the baseline patient characteristics in the treated and control groups are balanced after weighting.

IPTW is a particularly useful approach for this analysis given matching would result in the loss of patients from an already small sample size. Furthermore, as IPTW adjusts for a single scalar (i.e., the PS), rather than a full set of covariates, PS weighting methods are considered

appropriate when there are many covariates relative to the sample size and/or the number of events.

Due to the ability of IPTW to account for confounders present at baseline, whilst maintaining the sample size of the study, IPTW was utilised to reweight baseline characteristics in the base case analysis, to ensure a balance between the talquetamab cohort and the teclistamab cohort. For the reweighting approach, the estimated PSs were used to derive weights for each patient using estimand-specific weighting formulas (presented in Appendix B).

To explore the impact of using alternative adjustment methods, various methodologies outlined in NICE Technical Support Document 17, including multivariable regression and PS matching, were explored in sensitivity analyses (presented in Section 2.10.6).[172]

Weighting approaches

There are multiple weighting approaches available using IPTW; average effect of treatment in control group (ATC), average treatment effect (ATE) and average treatment effect for the treated (ATT) are the most commonly used. The ATE measures the average differences in outcomes between patients who receive the treatment of interest and those who do not, and ATT measures the average effect of the treatment for patients who have received the treatment. Conversely, the ATC measures the average effect of treatment for patients in the control group. Alternative approaches include average treatment effect on the overlap population (ATO) which measures the subset of the population where covariates of the treatment and control groups overlap.

To determine the most appropriate weighting methodology for this analysis, the relevance of the patient populations to the UK patient population in both trials was considered. The MajesTEC-1 trial, as presented in Table 23, was a Phase I/II study which included a cohort of TCE RRMM patients (Cohort A). While this population broadly aligned with the target population for talquetamab in this submission, the intervention in MajesTEC-1 was teclistamab. This is in contrast to MonumenTAL-1 which also included patients with TCE RRMM, however patients in MonumenTAL-1 were treated with talquetamab. As a result, MonumenTAL-1 was deemed to be the most representative of the population who would be eligible for talquetamab in the UK compared to the MajesTEC-1 cohort. The ATT approach to treatment weighting was therefore considered the most suitable methodology for adjustment, as it allows the baseline characteristics of the MajesTEC-1 cohort to be re-weighted to resemble those of MonumenTAL-1, thereby aligning with the population of relevance to this submission. UK clinical and health economic experts consulted in the preparation of this submission validated this approach.

Sensitivity analyses were conducted to explore uncertainty surrounding the weighting method used in the base case analysis and to assess the robustness of the selected approach. Alternative weightings, including the ATC, ATO and the ATE were explored and are presented in Section 2.10.6.

Further details of the ITC methods can be found in Appendix B.

2.10.2 Identification of covariates

The final list of covariates for the ITC in this submission is consistent with those presented (and accepted) in the teclistamab NICE submission [TA1015], which were selected based on several rounds of clinical validation meetings that the Company conducted for RRMM with multiple

clinical experts in July 2022, including previous validation exercises conducted to inform the cilta-cel submission [TA889]. This list of covariates was then further validated by four UK clinical experts consulted during interviews conducted for TA1015 in December 2023. In total, 17 potential covariates were identified of which 5 were deemed to be priority prognostic factors (Table 24). Given the availability of all 17 covariates in the data from MajesTEC-1 and MonumenTAL-1, these were all adjusted for, as reflected in Table 25 below, ensuring robustness of the ITC approach; this was highlighted as a key strength of the indirect evidence by HTA experts consulted by the Company.

Details of the validation study methodology can be found in Appendix B.

Table 24: Identification and ranking of prognostic factors for the ITC

Rank	Factor	Available in MajesTEC-1 & MonumenTAL-1
Priority	**Refractory status**	**ü**
Priority	**Cytogenetic profile**	**ü**
Priority	**ISS stage**	**ü**
Priority	**Time to progress on last regimen**	**ü**
Priority	**Extramedullary plasmacytoma**	**ü**
Non-priority	Number of prior LOTs	ü
Non-priority	Years since MM diagnosis	ü
Non-priority	Age	ü
Non-priority	Haemoglobin	ü
Non-priority	LDH levels	ü
Non-priority	Prior stem cell transplant	ü
Non-priority	ECOG Performance Status	ü
Non-priority	Race	ü
Non-priority	Sex	ü
Non-priority	Type of MM	ü
Non-priority	Creatinine levels	ü
Non-priority	Average duration of prior LOTs	ü

Abbreviations: ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; ITC: indirect treatment comparison; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma.

2.10.3 Assessment of overlap

The extent of overlap between the talquetamab and teclistamab patient populations was evaluated before and after adjustment. SMDs were used to evaluate the differences for each variable included in the analysis, with a SMD greater than 0.2 assumed to indicate a substantial difference between the populations.[173]

Before adjustment

SMDs calculated before adjustment are presented in Table 25 and depicted in Figure 15, while histograms of PSs are depicted in Figure 16. As presented in Table 25, and Figure 15, of the 17 prognostic variables adjusted for between MonumenTAL-1 and MajesTEC-1, 15 had an SMD ≤ ±0.2 prior to adjustment, suggesting there is a high level of alignment in the baseline characteristics of patients between the two cohorts. This alignment is to be expected as MonumenTAL-1 and MajesTEC-1 were conducted in the same licensed population (adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy), and additionally reduces the risk of selection bias.[174-176] As a result, a high degree of overlap was observed in the PS between the two cohorts prior to adjustment, with only two priority covariates (ISS level and EMD) falling outside the ±0.2 threshold. This emphasises the comparability of the patient groups in these trial cohorts. Consequently, given the high degree of overlap, truncation or trimming of the two trial cohorts prior to IPTW adjustment were not required. As detailed in Section 2.3.3, compared to the MajesTEC-1 cohort, patients in the MonumenTAL-1 cohort had moderately more advanced disease (as staged using the ISS and EMD) and were thus slightly harder to treat.

Additionally, HTA experts consulted by the Company commented that the ITC analyses presented were highly methodologically robust, and that the uncertainty surrounding the ITCs informing the NICE appraisal of teclistamab [TA1015] (in which IPD were not available for both patient populations) is not present.[3] This can be attributed to the fact that the ITC analyses in this appraisal compared two clinical trials, both sponsored by the Company with full access to IPD; meaning that patient characteristics were comprehensively captured and differences between the trials were expected to be minimal and able to be fully adjusted for in the ITC.[128, 129, 168, 177]

After adjustment

As noted previously, the ATT weighting approach was preferred in the current analysis.

Following the adjustment for the 17 variables, none of the variables had an SMD above the threshold of 0.2, indicating that the adjustment process successfully balanced characteristics between studies (see Table 25). These alignments between the populations are also evident in the histograms of the PSs, as shown in Figure 17.

Table 25: SMD for unadjusted and adjusted differences between MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort

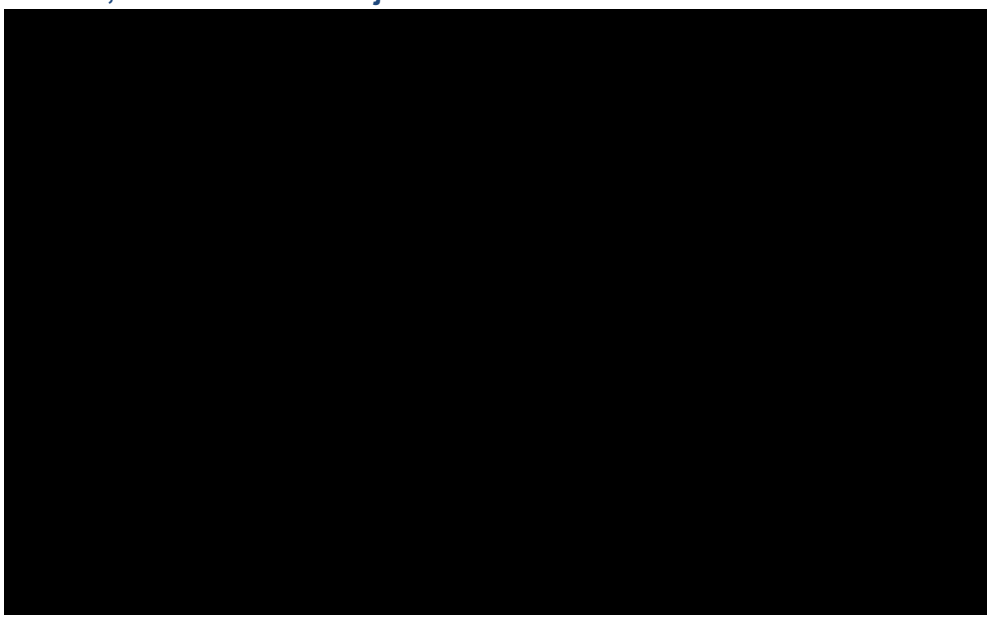
	Before adjustment			After adjustment		
	Talquetamab	Teclistamab	SMD	Talquetamab	Teclistamab	SMD
N	154	165	-	154	165	-
Refractory status, n (%)						
≤ double refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triple refractory	[redacted]	[redacted]		[redacted]	[redacted]	
Quad refractory	[redacted]	[redacted]		[redacted]	[redacted]	
≥ penta refractory	[redacted]	[redacted]		[redacted]	[redacted]	
ISS						
I	69 (44.8)	[redacted]	[redacted]	69 (44.8)	[redacted]	[redacted]
II	48 (31.2)	[redacted]		48 (31.2)	[redacted]	
III	37 (24)	[redacted]		37 (24)	[redacted]	
Time to progression on prior therapy						
<3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]		[redacted]	[redacted]	
Number of prior LOTs, n (%)						
≤4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]		[redacted]	[redacted]	
ECOG performance status, n (%)						
0	58 (37.7)	55 (33.3)	[redacted]	58 (37.7)	[redacted]	[redacted]
1+	96 (62.3)	110 (66.7)		96 (62.3)	[redacted]	
Age, n (%)						
<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]		[redacted]	[redacted]	
Gender, n (%)						

Male	90 (58.4)	96 (58.2)	[redacted]	90 (58.4)	[redacted]	[redacted]
Female	64 (41.6)	69 (41.8)		64 (41.6)	[redacted]	
Prior autologous stem cell transplantation, n (%)						
Yes	121 (78.6)	135 (81.8)	[redacted]	121 (78.6)	[redacted]	[redacted]
No	33 (21.4)	30 (18.2)		33 (21.4)	[redacted]	
Time (years) since diagnosis, n (%)						
<6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 years	[redacted]	[redacted]		[redacted]	[redacted]	
Average duration of prior lines of therapy (months), n (%)						
<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 to 14	[redacted]	[redacted]		[redacted]	[redacted]	
≥15	[redacted]	[redacted]		[redacted]	[redacted]	
Haemoglobin, n (%)						
<12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12+	[redacted]	[redacted]		[redacted]	[redacted]	
LDH, n (%)						
<280	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>280	[redacted]	[redacted]		[redacted]	[redacted]	
Creatinine clearance, n (%)						
<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-<90	[redacted]	[redacted]		[redacted]	[redacted]	
90+	[redacted]	[redacted]		[redacted]	[redacted]	
MM type, n (%)						
IgG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-IgG	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						

White	126 (81.8)	134 (81.2)	[redacted]	126 (81.8)	[redacted]	[redacted]
Other/not reported	28 (18.2)	31 (18.8)		28 (18.2)	[redacted]	
Cytogenetic risk, n (%)						
Standard risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
EMD, n (%)						
Yes	41 (26.6)	28 (17.0)	[redacted]	41 (26.6)	[redacted]	[redacted]
No	113 (73.4)	137 (83.0)		113 (73.4)	[redacted]	

Abbreviations: ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; IgG: immunoglobulin-G; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; SMD: standardised mean difference. **Source:** J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Moreau *et al*. 2022.[169]

Figure 15: SMDs between MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohorts, before and after adjustment



Footnotes: red triangle (unadjusted means), blue circle (ATT).
Abbreviations: ATT: average treatment effect for the treated; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; SMD: standardised mean difference.

Figure 16: Distribution of PSs before weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort

Abbreviations: PS: propensity score.

Figure 17: Distribution of PSs after ATT weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort

Abbreviations: ATT: average treatment effect for the treated; PS: propensity score.

2.10.4 Subsequent treatment adjustment

As described in Section 2.7, due to the international nature of the MonumenTAL-1 and MajesTEC-1 trials, some patients received some subsequent treatments which are not currently available in UK clinical practice (such as CAR-T cell therapies). Consequently, ITC analyses for OS were conducted where the MonumenTAL-1 and MajesTEC-1 data were adjusted using a two-stage adjustment in order to remove the effects of the subsequent treatments which are not routinely available, in line with the approach accepted by NICE in the appraisal for teclistamab [TA1015] (see the Base Case scenario in 2.10.6 below).[3] Full details of the two-stage adjustment are provided below.

Two-stage adjustment method

Initially, a simple adjustment method was implemented, where patients receiving a subsequent treatment that is not routinely available in the UK were artificially censored at time of initiation of this non-UK subsequent therapy (censoring method). The results produced were counterintuitive and lacked face validity (see Appendix J.1). As such, this censoring method was not considered further.

Consequently, in line with the approach taken in TA1015 for the calibration of the teclistamab extrapolations, a simplified two-stage method (as outlined in NICE TSD16) was used to adjust the OS KM data.[3, 164] The two-stage method compares patients who switched to treatments not routinely used in the UK and patients who switched to treatments that are routinely used in the UK who have had at least one subsequent treatment.

Using this method, the survival time was reduced for patients initiating a subsequent treatment which is not available in routine UK clinical practice.[178] The magnitude of the reduction was estimated by comparing survival times for patients who received subsequent treatments in MonumenTAL-1 which are not routinely available in the UK, versus patients who received subsequent treatments which are routinely available in the UK, starting from the secondary baseline defined as the first time the patient receives a non-UK treatment as part of their subsequent therapy for the first group, and as the start of first subsequent therapy for the latter. An accelerated failure time model was then used to estimate an acceleration factor – a parametric model with Weibull distribution adjusted by important prognostic factors measured at the new baseline (when available) was fitted. Refractory status, ISS status, extramedullary disease, cytogenetic risk, number of prior lines, years since diagnosis, age, haemoglobin, LDH, ECOG, time to progression in line prior switching were included. The resulting acceleration factor was then used to 'shrink' the survival times of patients receiving non-routine subsequent treatments.

A summary of the subsequent treatment regimens of patients in Cohort C of MonumenTAL-1 and in MajesTEC-1 before and after this two-stage adjustment are presented in Table 26 and Table 27, respectively. Given that talquetamab is not yet reimbursed, its use as a subsequent treatment following teclistamab does not reflect current UK clinical practice and so it was removed as a subsequent treatment option from MajesTEC-1 as part of the analyses. Additionally, the use of subsequent teclistamab following teclistamab treatment was also removed as an option in these analyses, as clinicians do not typically re-treat patients with therapies they have already relapsed on. Alternative scenarios exploring the use of subsequent teclistamab following talquetamab treatment, and subsequent talquetamab following teclistamab treatment are considered in Section 2.10.6.

Table 26: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, before subsequent treatment adjustment

Patients receiving subsequent therapy (%)	Talquetamab (MonumenTAL-1; Cohort C [N=[redacted][a]])	Patients receiving subsequent therapy (%)	Teclistamab (MajesTEC-1 [N=[redacted][b]])
UK relevant subsequent treatments			
Bendamustine-based regimens	[redacted]	Bendamustine based regimens	[redacted]
Bortezomib plus chemotherapy	[redacted]	Bortezomib plus chemotherapy	[redacted]
Cisplatin plus chemotherapy	[redacted]	Cisplatin based regimens	[redacted]
Cyclophosphamide-based regimens	[redacted]	Cyclophosphamide based regimens	[redacted]
Pomalidomide-based regimens	[redacted]	Cytarabine based	[redacted]
Dexamethasone monotherapy	[redacted]	Dexamethasone monotherapy	[redacted]
Melphalan-based regimens	[redacted]	Doxorubicin based	[redacted]
Lenalidomide monotherapy	[redacted]	Melphalan-based regimens	[redacted]
Methylprednisolone monotherapy	[redacted]	Pomalidomide-based regimens	[redacted]

Selinexor	[redacted]	Selinexor	[redacted]
Teclistamab monotherapy	[redacted]	Thalidomide-based	[redacted]
Non-UK relevant subsequent treatments[c]			
Belantamab-based regimens	[redacted]	Belantamab-based regimens	[redacted]
Bendamustine-based regimens	[redacted]	Bortezomib plus chemotherapy	[redacted]
Bortezomib plus chemotherapy	[redacted]	CAR-T cell therapies	[redacted]
CAR-T cell therapies	[redacted]	Carfilzomib plus chemotherapy	[redacted]
Carfilzomib plus chemotherapy	[redacted]	Daratumumab based regimens	[redacted]
Cevostamab plus chemotherapy	[redacted]	Elotuzumab based regimens	[redacted]
Ciltacabtagene autoleucel-based regimens	[redacted]	Etoposide based regimens	[redacted]
Cyclophosphamide-based regimens	[redacted]	Melflufen plus dexamethasone	[redacted]
Daratumumab-based regimens	[redacted]	Pomalidomide based regimens	[redacted]
Dexamethasone-based regimens	[redacted]	Talquetamab	[redacted]
Idecabtagene vicleucel	[redacted]	Teclistamab	[redacted]
Investigational antineoplastic drugs	[redacted]	Venetoclax	[redacted]
Linvoseltamab-based regimens	[redacted]	Other investigational agents[d]	[redacted]
Venetoclax	[redacted]		

Footnotes: [a] The percentage of patients receiving cyclophosphamide-based regimens, bortezomib-based regimens and bendamustine-based regimens represents the percentage of patients receiving both UK-relevant and non-UK relevant forms of each regimen, as presented in Table 22.
[b] Total N refers to patients who survived progression who started at least one subsequent on or after progression date
[c] This summary of non-UK relevant subsequent treatments only presents treatments received by >1 patient. A table of the full subsequent treatment distribution in MonumenTAL-1 is presented in Appendix L
[d] Other investigational agents include investigational antineoplastic drugs, investigational drug, BFCR 4350A, BFCR 4350A-dexamethasone, CC 92480-dexamethasone, tasquinimod, TAK 573 and monoclonal antibodies
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO);[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]

Table 27: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, after subsequent treatment adjustment (re-weighted to adjust for treatments not relevant to UK clinical practice)

Patients receiving subsequent therapy (%)	Talquetamab (MonumenTAL-1; Cohort C)[a]	Patients receiving subsequent therapy (%)	Teclistamab (MajesTEC-1)[a]

Bendamustine-based regimens	[redacted]	Bendamustine-based regimens	[redacted]
Bortezomib plus chemotherapy	[redacted]	Bortezomib plus chemotherapy	[redacted]
Cisplatin plus chemotherapy	[redacted]	Cisplatin plus chemotherapy	[redacted]
Cyclophosphamide-based regimens	[redacted]	Cyclophosphamide-based regimens	[redacted]
Pomalidomide-based regimens	[redacted]	Pomalidomide-based regimens	[redacted]
Dexamethasone monotherapy	[redacted]	Dexamethasone monotherapy	[redacted]
Melphalan-based regimens	[redacted]	Dexamethasone plus vincristine plus doxorubicin	[redacted]
Lenalidomide monotherapy	[redacted]	Melphalan-based regimens	[redacted]
Methylprednisolone monotherapy	[redacted]	Selinexor	[redacted]
Selinexor monotherapy	[redacted]		
Teclistamab monotherapy	[redacted]		

Footnotes: [a]Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO);[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]

2.10.5 Results

Response outcomes

After ATT adjustment, the results of the ITC showed that talquetamab demonstrates a greater breadth of response compared to teclistamab, with an ORR that was significantly higher. Talquetamab also exhibited comparable depth and duration of response to teclistamab. Further details on these response outcomes are presented below.

ORR

The estimated response rates for talquetamab compared to teclistamab, before and after adjustment are presented in Figure 18 and the estimated RR from the comparison are presented in Table 28.

Following ATT adjustment, patients receiving talquetamab had a significantly higher likelihood of experiencing an overall response (RR: [redacted] [95% CI: [redacted]; p=[redacted]) compared to patients receiving teclistamab.

The likelihood of achieving a ≥CR or ≥VGPR+ (RR: [redacted] [95% CI: [redacted]; p=[redacted] and RR: [redacted] [95% CI: [redacted]; p=[redacted])) was comparable for patients receiving talquetamab and teclistamab following ATT adjustment, suggesting that they elicit a similar response depth in patients with TCE RRMM.

Table 28: ORR results of the ITC between talquetamab and teclistamab (before and after ATT weighting)

Comparison	ORR RR (95% CI)	p-value	≥VGPR RR (95% CI)	p-value	≥CR RR (95% CI)	p-value
Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighting						
ATT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; CR: complete response; ITC: indirect treatment comparison; ORR: overall response rate; RR: relative risks; VPGR: very good partial response.

Figure 18: Response rates for talquetamab and teclistamab (before and after ATT weighting)

[redacted]

Abbreviations: ATT: average treatment effect for the treated; CR+: complete response or better; ORR: overall response rate; PR: partial response; RR: risk ratio; VGPR: very good partial response.

DoR

The KM curve for DoR for talquetamab, alongside the unadjusted and ATT-reweighted KM curves for teclistamab are presented in Figure 19, and the estimates of the DoR treatment effect for talquetamab relative to teclistamab before and after adjustment are presented in Table 29.

The median DoR in patients receiving talquetamab was [redacted] months (95% CI: [redacted]), while the ATT-adjusted median DoR for patients receiving teclistamab was higher, at [redacted] months (95% CI: [redacted]). The ATT-adjusted ITC results (HR: [redacted]; 95% CI: [redacted]) indicates that the DoR for talquetamab and teclistamab are comparable.

Figure 19: DoR KM curves for talquetamab and teclistamab (before and after ATT weighting)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; DoR: duration of response; IRC: independent review committee; KM: Kaplan-Meier; NE: not estimable.

Table 29: DoR results of the ITC between talquetamab and teclistamab (before and after ATT weighting)

Comparison	DoR HR (95% CI)	p-value
Naïve	[redacted]	[redacted]
Weighting		
ATT	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; DoR: duration of response; HR: hazard ratio; ITC: indirect treatment comparison.

Survival outcomes

Progression-free survival

The PFS KM curve for talquetamab alongside the unadjusted and ATT-reweighted KM curve for teclistamab is presented in Figure 20. The estimates of the PFS treatment effect for talquetamab relative to teclistamab after adjustment are presented in Table 30.

The PFS KM curves for talquetamab and ATT-adjusted teclistamab show [redacted] The results demonstrate that treatment with talquetamab resulted in comparable PFS compared to treatment with teclistamab (PFS HR [redacted] [95% CI [redacted]] p=[redacted]).

Figure 20: PFS KM curves for talquetamab (before and after ATT weighting) and teclistamab

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; IRC: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival.

Table 30: PFS results of the ITC between talquetamab and teclistamab (before and after ATT weighting)

Comparison	PFS HR (95% CI)	p-value
Naïve	[redacted]	[redacted]
Weighting		
ATT	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; PFS: progression-free survival.

Overall survival

The OS KM curve for talquetamab alongside the unadjusted and ATT-reweighted KM curve for teclistamab is presented in Figure 21. The estimates of the OS treatment effect for talquetamab relative to teclistamab after adjustment are presented in Table 31.

Treatment with talquetamab provided meaningful improvements to patient survival when compared to those treated with teclistamab (OS HR [redacted] [95% CI [redacted]]; **the hazard of death was reduced by [redacted] when compared to teclistamab.** Median OS was [redacted] ([redacted] (95% CI [redacted]) in the talquetamab group versus [redacted] (95% CI [redacted]) for ATT-adjusted teclistamab, after similar periods of follow up of 31.2 months and 30.4 months of median follow-up, respectively.[119] As seen in Figure 21, [redacted]. At 24-months [redacted]% (95% CI[redacted]) of patients who received talquetamab were alive, in comparison to [redacted]% of those in the ATT-adjusted teclistamab group.

Figure 21: OS KM curves for talquetamab and teclistamab (before and after ATT weighting)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; NE: not estimable; OS: overall survival.

Table 31: OS results of the ITC between talquetamab and teclistamab (before and after ATT weighting)

Comparison	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]
Weighting		
ATT	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival.

Overall survival (following subsequent treatment adjustment)

Base case

The OS KM curves for talquetamab and ATT-adjusted teclistamab, following the subsequent treatment adjustment are presented in Figure 22. As part of the adjustment in this analysis, talquetamab was removed as a subsequent treatment from MajesTEC-1, but teclistamab was retained as a subsequent treatment in MonumenTAL-1, thus reflecting current UK clinical practice, in which talquetamab is not yet reimbursed. This analysis shows that after the exclusion of subsequent treatments not available in UK clinical practice, talquetamab reduces the risk of death by [redacted]% compared to teclistamab (HR: [redacted] [95% CI: [redacted]], p[redacted]), consistent with the ITC analysis prior to the subsequent treatment adjustment.

Figure 22: OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; NE: not estimable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

Table 32: OS results of the ITC between talquetamab and teclistamab in the economic model base case scenario (before and after ATT weighting and subsequent treatment adjustment adjustment)

Comparison	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]

ATT (main ITC)	[redacted]	[redacted]
Base case scenario (for economic model)	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival.

2.10.6 Sensitivity results

Scenario analyses: impact of varying the distribution of subsequent therapies

To contextualise the OS results in the main ITC and Base case analysis, additional scenario analyses was conducted to explore the potential impact of distinct distribution of subsequent therapies between patients in MonumenTAL-1 and MajesTEC-1, the details of which are outlined below.

Scenario 1 (removal of BsAbs as subsequent treatments in both arms, "All-Out")

In this scenario, OS was similarly adjusted such that subsequent treatments not available in UK clinical practice were removed. In addition to this, subsequent use of teclistamab was also removed from MonumenTAL-1 in this scenario (i.e., patients who have progressed on talquetamab were not allowed to receive teclistamab). Whilst this does not reflect anticipated UK clinical practice following the recommendation of talquetamab, this scenario explored the robustness of the OS benefit to removal of all BsAbs as subsequent treatment following either talquetamab or teclistamab and provides a 'like-for-like' comparison of talquetamab and teclistamab, without differences in the availability of effective subsequent BsAbs treatments potentially driving any observed benefits. The distribution of subsequent therapies for patients in MonumenTAL-1 and MajesTEC-1 in this scenario are presented in Appendix M.

The OS KM curves for talquetamab and ATT-adjusted teclistamab, in Scenario 1 are presented in Figure 23. This analysis demonstrates that the OS benefit for talquetamab (HR: [redacted][95% CI: [redacted]], p[redacted]) is observed regardless of availability of teclistamab as a subsequent treatment in MonumenTAL-1.

Figure 23: OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice and further excluding the availability of subsequent teclistamab or talquetamab in both treatment arms

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; NE: not estimable; OS: overall survival.

Table 33: OS results of the ITC between talquetamab and teclistamab in the All-Out scenario (before and after ATT weighting and subsequent treatment adjustment adjustment)

Comparison	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]
ATT (main ITC)	[redacted]	[redacted]
ATT + subsequent treatment adjustment + removal of talquetamab post-teclistamab and teclistamab post-talquetamab ('All-Out' Scenario)	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival.

Scenario 2 (The inclusion of BsAbs as subsequent treatments in both treatment arms; potential future UK clinical practice; "All-In")

In this second scenario, OS was adjusted similarly by removing subsequent treatments that are not available in UK clinical practice. However, the subsequent use of talquetamab following

teclistamab was permitted, as was the subsequent use of teclistamab after talquetamab. This scenario simulates potential future UK clinical practice, should talquetamab be recommended, allowing clinicians to sequence the 2 bispecific therapies interchangeably to further extend survival benefits for their patients. The distribution of subsequent therapies for patients in MonumenTAL-1 and MajesTEC-1 in this scenario are presented in Appendix M.

The OS KM curves for talquetamab and ATT-adjusted teclistamab are presented in Figure 24. This analysis demonstrates that talquetamab reduces the risk of death by [redacted]% compared to teclistamab (HR: [redacted][95% CI: [redacted]], p[redacted]).

Figure 24: OS KM curves for talquetamab and ATT-weighted teclistamab (potential future UK clinical practice), i.e. following subsequent treatment adjustment to reflect current UK clinical practice and further inclusion of subsequent teclistamab and talquetamab

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; NE: not estimable; OS: overall survival.

Table 34: OS results of the ITC between talquetamab and teclistamab in the All-In scenario (before and after ATT weighting and subsequent treatment adjustment adjustment)

Comparison	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]
ATT (main ITC)	[redacted]	[redacted]

ATT + subsequent treatment adjustment + inclusion of talquetamab post-teclistamab and teclistamab post-talquetamab (All-In Scenario)	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival.

Summary of the subsequent therapy distribution scenarios

A summary of the scenario analyses assessing the impact of varying the distribution of subsequent therapies is presented in Table 35 below.

These additional analyses demonstrate that the OS benefit associated with talquetamab is consistently observed across all analyses performed, irrespective of the distribution of subsequent therapies. This finding underscores the robustness of the OS benefit associated with talquetamab compared to teclistamab, as it remains significant irrespective of the subsequent treatment distributions that were explored in each scenario, suggesting that the observed benefit is not solely attributed to differences in the subsequent treatments received in MonumenTAL-1 and MajesTEC-1.

Table 35: Overview of OS ITC analyses, including adjustment for subsequent treatments

Analysis	Scenario	Subsequent treatment allowed	Rationale	HR (95%CI); p-value)
Unadjusted ITC	-	All subsequent treatments allowed, including treatment not available in the UK	-	[redacted]
ATT weighted (main ITC)		All subsequent treatments allowed, including treatment not available in the UK	To explore the impact of IPTW with ATT weights on the OS results	[redacted]
OS adjustment based on subsequent therapies (ATT-weighting)	Base case	Restricted to current UK treatments, including: TEC allowed post-TAL No TAL allowed post-TEC	To remove the effect of non-routine UK treatments on OS and thereby reflect **current UK clinical practice**, wherein BsAbs such as talquetamab would not be available post-teclistamab	[redacted]
	Scenario 1 (“All-out”)	Restricted to current UK treatments, in addition to: No TEC allowed post-TAL No TAL allowed post-TEC	**This scenario does not reflect anticipated UK clinical practice but is an illustrative scenario** to explore robustness of the OS benefit with removal of all BsAbs as subsequent treatment following either talquetamab or teclistamab.	[redacted]

	Scenario 2 ("All-in")	Restricted to UK treatments, in addition to: TEC allowed post-TAL TAL allowed post-TEC	To remove the effect of non-routine UK treatment on OS but reflect **potential future UK clinical practice** if talquetamab is recommended, wherein patients who have progressed on teclistamab can receive talquetamab.	[redacted]

Footnotes: ATT: average treatment for the treated; BsAbs: bi-specific antibodies; HR: hazard ratio; OS: overall survival; TAL: talquetamab; TEC: teclistamab; UK: United Kingdom.

Alternative weightings

The results of the sensitivity analyses exploring various alternative IPTW weightings (e.g., ATC, ATE, ATO) and different ITC approaches as recommended in NICE TSD 17 (i.e., multivariate regression, PS matching), using 17 adjustment variables in line with the base case approach are presented for PFS and OS in Table 36.[172]

The results demonstrate that all the plausible ITC methodologies, including the main IPTW ATT-weighting approach, are broadly comparable with no marked differences in the resultant adjusted HRs for both PFS and OS and consistent conclusions on the comparative effectiveness of talquetamab and teclistamab.

Statistically significant differences were observed in all adjusted OS HRs between talquetamab and teclistamab, across all ITC analyses. OS HRs were highly consistent across ITC analyses and all [redacted], strongly supporting the consistent survival benefit that talquetamab provides. This suggests that the observed OS benefit of talquetamab over teclistamab does not result from the ITC weighting approach used, and is [redacted]

Table 36: Base case sensitivity analysis for PFS and OS

Comparison	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
Weighting				
ATT (main ITC)	[redacted]	[redacted]	[redacted]	[redacted]
ATC	[redacted]	[redacted]	[redacted]	[redacted]
ATO	[redacted]	[redacted]	[redacted]	[redacted]
ATE	[redacted]	[redacted]	[redacted]	[redacted]
Multivariate regression	[redacted]	[redacted]	[redacted]	[redacted]
PS matching	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The IPTW analyses adjusted for 17 covariates.
Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATT: average treatment effect for the treated population; ATO: treatment effect on the overlap population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival.

Accounting for the talquetamab QW dosing regimen

As highlighted in Section 2.3.1, Cohort C represents the population of most relevance to this submission, as clinical feedback indicates that the majority of patients in UK clinical practice will

likely receive the Q2W regimen due to the reduced requirement for hospital visits and hence improved convenience over the weekly regimen. However, clinician estimates suggested that approximately 10% of patients would still receive the QW dosing regimen in practice (represented by Cohort A in the MonumenTAL-1 trial), with the remaining 90% receiving the Q2W dosing regimen.

To account for this, the Company performed additional ITC sensitivity analyses comparing talquetamab (using data from a combination of patients from Cohorts A+C in MonumenTAL-1, with patients in each cohort weighted as per the 10%:90% split suggested by clinical experts) versus teclistamab, the results of which are presented in Table 37. Additional results and KM curves from this comparison are presented in Appendix M.2.

These results demonstrate that the PFS and OS estimates utilising the weighted combined Cohort A+C for talquetamab are comparable to the results when using only Cohort C from MonumenTAL-1. PFS is similar for talquetamab (weighted Cohort A+C) and teclistamab (HR: [redacted] [95% CI [redacted]; p=[redacted]) while, in consistency with the main ITC, OS is extended compared to teclistamab (HR: [redacted] [95% CI [redacted], p<[redacted]). The consistency of the OS results in this sensitivity analysis demonstrate the robustness of the OS benefit in favour of talquetamab.

Table 37: Alternative dosing regimen sensitivity analysis results

ITC	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Talquetamab (Cohort C) versus teclistamab				
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
ATT (main ITC)	[redacted]	[redacted]	[redacted]	[redacted]
Talquetamab (Cohort A+C; weighted 10:90 as per clinical expert feedback) versus teclistamab				
Naïve	[redacted]	[redacted]	[redacted]	[redacted]
ATT (main ITC)	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The ATT and ATC analyses adjusted for all 17 covariates.
Abbreviations: ATC: average treatment effect for the control; ATT: average treatment effect for the treated population; CI: confidence interval; DoR: duration of response; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RR: relative risk.

2.10.7 Uncertainties in the indirect and mixed treatment comparison

Comparability of the trial populations

ITCs derived from single-arm trials inherently carry a degree of uncertainty, as they are reliant on the assumption that all prognostic factors and treatment effect variables can be adequately adjusted to ensure the validity of the results.

However, the uncertainty associated with the ITC presented in this submission is deemed minimal. As discussed in Section 2.10.3, the similarities in trial design between MonumenTAL-1 and MajesTEC-1, along with the availability of IPD from both trials, allowed for the ATT adjustment of the MajesTEC-1 baseline characteristics across all 17 key covariates identified by

clinical experts. Consequently, differences between the trials were expected to be minimal and were fully adjusted for in the ITC. The ATT adjustment resulted in SMDs <0.2 for all variables, enhancing the comparability of the two cohorts. HTA experts consulted by the Company acknowledged that the ITC approach was highly robust and in line with the best practices outlined by NICE.[120] As such, this trial-vs-trial ITC represents the most appropriate evidence for the comparison of the efficacy of talquetamab and teclistamab.

Generalisability

The international context of the MonumenTAL-1 and MajesTEC-1 clinical trials potentially introduces some uncertainty regarding the generalisability of the trial populations to TCE RRMM patients in the NHS. MajesTEC-1 was previously deemed acceptable by NICE for decision-making in the UK as part of TA1015 and clinical experts consulted ahead of the talquetamab submission indicated that the patient population in MonumenTAL-1 is similarly generalisable to UK clinical practice.[3] Therefore, despite the international scope of both trials, the clinical results are expected to be generalisable to the UK setting, thus providing further validity to the comparative evidence base.

Subsequent therapies

It could be hypothesised that the observed OS benefit in favour of talquetamab is attributed to differences in the distribution of subsequent treatments among patients in MonumenTAL-1 and MajesTEC-1, and/or the use of subsequent therapies not routinely administered in UK clinical practice across the two trials. Variations in subsequent treatments could impact patient survival and consequently impact the results of the ITC. However, as presented in Section 2.10.6, the scenario analyses adjusting for these disparities demonstrated that the OS benefit in favour of talquetamab occurred consistently, even following the exclusion of BsAb therapies and all non-routine subsequent treatments in both treatment arm. Therefore, the observed OS benefit with talquetamab cannot be solely attributed to the effects of subsequent therapies. Therefore, the comparative evidence for talquetamab and teclistamab indicates that there is a [redacted]

Additional sensitivity analysis

The observed OS benefit for talquetamab over teclistamab was also consistent across an extensive range of sensitivity analyses including alternative weighting, multivariate regression and PS matching, with all OS HRs [redacted]. This therefore strongly supports the consistent survival benefit that talquetamab provides over teclistamab in the TCE RRMM patient population. Additional sensitivity analyses using the combined Cohort A+C (weighted 10:90 as per clinical expert feedback) for talquetamab compared with teclistamab, were consistent with the main ITC, thus also demonstrating the robustness of the results and the validity of the OS benefit of talquetamab (HR: [redacted] [95% CI [redacted], p<[redacted]).

2.10.8 Conclusions of the indirect and mixed treatment comparisons

Overall, the trial-vs-trial ITCs discussed above demonstrate that talquetamab is a highly effective treatment option for patients with TCE RRMM, resulting in comparable DoR and PFS along with a significantly greater ORR and OS when compared to teclistamab. The introduction of

teclistamab represented a step change in the treatment paradigm for patients with TCE RRMM in UK clinical practice, with an approximate 50% reduction in the risk of death when compared to the historical standards of care in this setting. However, as detailed in Section 1.3.3, RRMM remains an incurable disease and patients will inevitably experience disease progress on their treatments.

The introduction of talquetamab would represent another step forward in the treatment paradigm. In the 'All-In' scenario presented in Section 2.10.6 (in which the effect of non-UK subsequent treatments was removed, but the use of subsequent BsAb treatment was included for both talquetamab and teclistamab), demonstrated that this OS benefit is expected to be maintained in future UK clinical practice (HR: [redacted] [95% CI, [redacted], p=[redacted]).

The consistency of the OS benefit of talquetamab across the various sensitivity analyses conducted in Section 2.10.6 demonstrated that the OS benefit cannot be solely attributed to differences in the subsequent treatment distributions of patients in MonumenTAL-1 and MajesTEC-1. To conclude, these ITC results therefore demonstrate that talquetamab represents an efficacious treatment option for TCE RRMM patients, that will result in improvements in survival for TCE RRMM patients.

2.11 Adverse reactions

2.11.1 Treatment duration and dosage

A summary of treatment duration and dose intensity of patients receiving talquetamab in MonumenTAL-1 is provided in Table 38. The median (range) duration of talquetamab for patients in Cohort C (0.8 mg/kg Q2W) was [redacted] months ([redacted] months), with a median (range) dose intensity across all treatment cycles of [redacted] µg/kg/week ([redacted]µg/kg/week).[46]

Table 38: Summary of the treatment duration and dose intensity in patients receiving talquetamab; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

	Cohort C (0.8 mg/kg Q2W)
Duration of talquetamab (months)	N=154
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Dose intensity (All treatment cycles, µg/kg/week)[a]	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Number of doses	N=154
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]

[a] Dose intensity (µg/kg/week) was calculated as the sum of total treatment doses (µg/kg) received (excluding Step-up doses prior to Cycle 1, any Step-up doses that were received after Cycle 1 are considered) divided by the protocol specified cycle length in weeks on talquetamab after step-up dosing period.
Abbreviations: DCO: data cut-off; RP2D: recommended Phase II dose; Q2W: biweekly; SD: standard deviation.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.11.2 Summary of treatment-emergent adverse events

A summary of the TEAE in Cohort C (0.8 mg/kg Q2W) is provided in Table 39. At least one TEAE was experienced by [redacted] of patients in Cohort C of the MonumenTAL-1 trial, with [redacted] of patients experiencing at least one TEAE that was judged as being related to talquetamab.[46]

Serious TEAE(s) were reported in [redacted]% of patients, and [redacted]% of patients in Cohort C were judged by the investigator to have experienced serious TEAEs that were related to talquetamab.[46] Maximum Grade 3 TEAE(s) were reported for [redacted]%, maximum Grade 4 TEAE(s) were reported for [redacted]% of patients and maximum Grade 5 TEAE(s) were reported for [redacted]% of patients.[46]

Additionally, [redacted]% of patients experienced a TEAE with an outcome of death.[46] The causes of death in MonumenTAL-1 and MajesTEC-1 are discussed in further detail in Section 2.11.5. Importantly, the rates of TEAEs leading to discontinuation were low in Cohort C, with only [redacted] patients ([redacted]%) discontinuing due to a TEAE.[46] This low rate of discontinuation indicates that the overall safety profile of talquetamab is manageable.

Table 39: Summary of treatment-emergent adverse events; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

TEAEs, N (%)	Cohort C (0.8 mg/kg Q2W) [N=154]
TEAE leading to discontinuation of talquetamab[a]	[redacted]
Any TEAE	[redacted]
Study drug-related[b]	[redacted]
Maximum toxicity grade	
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Grade 5	[redacted]
Any serious TEAE	[redacted]
Study drug-related[b]	[redacted]
TEAE with outcome death[c]	[redacted]

Footnotes: [a] Includes those patients indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page. [b] TEAEs related to study drug. [c] TEAE with outcome death on the AE eCRF page.
Abbreviations: AE: adverse event; DCO: data cut-off; Q2W: biweekly; TEAE: treatment-emergent adverse event.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]

2.11.3 Most common treatment-emergent adverse events

A summary of the most common TEAEs of any grade occurring in ≥10% of patients in Cohort C (0.8 mg/kg Q2W) is presented in Table 40. The most common TEAEs of any grade were CRS and dysgeusia occurring in 75.3% and [redacted]% of patients, respectively.[46, 119] However, only 1 case of CRS was ≥grade 3, and dysgeusia has a maximum grade of 2, demonstrating that, although these AEs occurred frequently, they were generally low in severity and manageable.[119]

Table 40: Summary of most common (≥10%) TEAEs of any grade; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)

Any Grade TEAEs, N (%)	Cohort C (0.8 mg/kg Q2W) [N=154]
Nervous system disorders	[redacted]
Dysgeusia	[redacted]
Ageusia	[redacted]
Headache	[redacted]
Dizziness	[redacted]
Immune effector cell-associated neurotoxicity syndrome	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Skin exfoliation	[redacted]
Dry skin	[redacted]
Pruritus	[redacted]
Nail disorder	[redacted]
Onychomadesis	[redacted]
Rash	[redacted]
Alopecia	[redacted]
Rash maculo-papular	[redacted]
Gastrointestinal disorders	[redacted]
Dry mouth	60 (39.0)
Diarrhoea	[redacted]
Dysphagia	[redacted]
Constipation	[redacted]
Nausea	[redacted]
Vomiting	[redacted]
Immune system disorders	[redacted]
Cytokine release syndrome	116 (75.3)
Blood and lymphatic system disorders	[redacted]
Anaemia	67 (43.5)
Lymphopenia	[redacted]
Thrombocytopenia	46 (29.9)
Neutropenia	44 (28.6)
Leukopenia	[redacted]
Infections and infestations	109 (70.8)
COVID-19	[redacted]
Upper respiratory tract infection	[redacted]
Metabolism and nutrition disorders	[redacted]
Decreased appetite	[redacted]
Hypokalaemia	[redacted]
Hypophosphataemia	[redacted]
Hypomagnesaemia	[redacted]

Any Grade TEAEs, N (%)	Cohort C (0.8 mg/kg Q2W) [N=154]
Hypocalcaemia	[redacted]
Hyponatraemia	[redacted]
Hypoalbuminaemia	[redacted]
General disorders and administration site conditions	[redacted]
Fatigue	44 (28.6)
Pyrexia	44 (28.6)
Asthenia	[redacted]
Oedema peripheral	[redacted]
Investigations	[redacted]
Weight decreased	64 (41.6)
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
C-reactive protein increased	[redacted]
Blood alkaline phosphatase increased	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
Pain in extremity	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Cough	[redacted]
Oropharyngeal pain	[redacted]
Psychiatric disorders	[redacted]
Insomnia	[redacted]
Vascular disorders	[redacted]
Hypertension	[redacted]
Hypotension	[redacted]

Footnotes: [a] ICANS was only measured in the phase 2 cohort in which the denominator is 118 patients.
Abbreviations: CRS: cytokine release syndrome; DCO: data cut-off; Q2W: biweekly; TEAE: treatment-emergent adverse event.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119] Chari *et al.* 2025.[117]

The most common Grade 3/4 TEAEs occurring in at least 5% of patients in Cohort C were lymphopenia and anaemia occurring in [redacted]% and 25.3% of patients, respectively.[119] A naïve side-by-side comparison with that of patients receiving teclistamab in MajesTEC-1 [N=165] is presented in Table 41. A higher proportion of patients who experienced ≥1 Grade 3/4 TEAE was observed in MajesTEC-1 compared to MonumenTAL-1, in particular a higher proportion of patients experienced TEAEs with the nature of blood and lymphatic system disorders in MajesTEC-1 at [redacted] compared to [redacted] in MonumenTAL-1.[40, 46]

Treatment with BCMA-targeting BsAbs result in the elimination of BCMA-expressing plasma cells and the disruption of BCMA signalling, which further impacts plasma cell survival and proliferation.[179] BsAb-targeted therapy is associated with significant neutropenia, lymphopenia, and hypogammaglobulinemia, directly increasing the risk of acquiring bacterial, fungal, and viral infections via the stimulation of regulatory T cells.[180] In addition, T cell activation can lead to cytokine release which may affect bone marrow and haematopoiesis.[181]

Table 41: Most common (≥5%) Grade 3 or 4 TEAEs for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

Grade 3 or 4 TEAEs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Patients with ≥1 Grade 3 or 4 TEAE	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Anaemia	39 (25.3)	[redacted]
Neutropenia	33 (21.4)	[redacted]
Thrombocytopenia	28 (18.2)	[redacted]
Leukopenia	[redacted]	[redacted]
Metabolism and Nutrition Disorders	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight decreased	9 (5.8)	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; Q2W: biweekly; TEAE: treatment-emergent adverse event.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO);[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

2.11.4 Adverse events of special interest

Adverse events of special interest (AESIs) were reported in MonumenTAL-1; these can be broadly categorised into (1) BsAb-specific AEs (i.e., CRS and ICANS) (2) GPRC5D-specific AEs and (3) infections. The outcomes of the AESIs in MonumenTAL-1 indicated that talquetamab is well tolerated with predictable AEs similar to the AE profile of other BsAbs, manageable GPRC5D-specific AEs (e.g., weight loss, dysgeusia, skin/nail disorders) and improved infection-related safety outcomes when compared to teclistamab.

A naïve side-by-side comparison of AESI incidence for talquetamab and teclistamab based on MonumenTAL-1 Cohort C (September 2024 DCO) and MajesTEC-1 (August 2023 DCO) respectively, are presented in the subsequent sections.

BsAb-specific AEs

CRS

CRS is an AESI known to be associated with T-cell engaging BsAbs, which can lead to rapid activation of the immune system and cytokine release. A summary of CRS experienced by patients receiving talquetamab and teclistamab is presented in Table 42. The incidence of CRS was largely comparable across MonumenTAL-1 and MajesTEC-1.

While CRS of all grades occurred in 75.3% of patients receiving talquetamab, almost all of these events were manageable – with **only one patient (0.6%)** experiencing Grade 3/4 CRS and [redacted] fatal outcomes.[46, 119] CRS was adequately managed with dose modifications – while [redacted] patients ([redacted]%) had their talquetamab dose modified as a result of CRS, only [redacted] patient ([redacted]%) had to discontinue talquetamab due to CRS. The low rates of drug discontinuation and modification highlight that CRS associated with talquetamab could be adequately managed in clinical practice.[46]

A similar incidence proportion of CRS of all grades occurred in [redacted]% of patients receiving teclistamab - all of these events were manageable, with [redacted] patients ([redacted]%) having their teclistamab dose modified and no patients discontinuing as a result of CRS.[46]

Table 42: CRS for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
CRS (any grade)	116 (75.3)	[redacted]
Grade 3/4	1 (0.6)	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; CRS: cytokine release syndrome; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

Neurotoxicity

ICANS is another TEAE frequently associated with BCMA-targeting BsAbs which is also observed with talquetamab. A summary of ICANS in patients in Cohort C of MonumenTAL-1 is presented in Table 43. Similar to CRS, incidence of ICANS remain largely comparable across MonumenTAL-1 and MajesTEC-1 with a small increase in the proportion patients experiencing ICANS in MonumenTAL-1.

ICANS of any grade occurred in [redacted] ([redacted]%) of patients receiving talquetamab in Cohort C of MonumenTAL-1, but only [redacted]% of patients experienced Grade 3/4 ICANS, [redacted] patients ([redacted]%) who required dose modification and [redacted] patient ([redacted]%) who discontinued talquetamab due to ICANS.[46] There were [redacted] fatal outcomes; when considered alongside the low rates of drug discontinuation and modification, this demonstrates that ICANS events can be generally well managed in clinical practice.[46]

A similar incidence proportion of ICANS of any grade occurred in [redacted] ([redacted]%) patients receiving teclistamab in MajesTEC-1, with [redacted] patient ([redacted]%) having their teclistamab dose modified and [redacted] fatal outcomes.[40]

Table 43: ICANS for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=118][a]	MajesTEC-1 [N=165]
ICANS (any grade)	[redacted]	[redacted]
Grade 3/4	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[b]	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a] Data on ICANS incidence was only collected during the Phase II portion of MonumenTAL-1 (N=118). As such the percentages in Table 43 use N=118 as a denominator. [b]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; ICANS: immune effector cell-associated neurotoxicity syndrome; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Chari *et al.* 2025.[117]

GPRC5D-related AESIs

Talquetamab is a GPRC5D-targeting BsAb therapy, and therefore as expected the incidence of GPRC5D-related AESIs was higher for talquetamab as opposed to teclistamab, a BCMA-targeting BsAb. GPRC5D-related AESIs reported in MonumenTAL-1 included dysgeusia and weight loss, skin disorders, rash and nail disorders, all of which were well-managed with [redacted] of these events leading to fatal outcomes and few leading to discontinuations or dose reductions as reported in detail below. This highlights that similar to AEs observed in other haematological conditions, these GPRC5D-related AESIs are manageable. Appropriate supportive measures, such as nutritional risk assessment and dietician engagement can be pre-emptively put in place to further mitigate the incidence of these expected AESIs.

For completeness, a side-by-side comparison for the abovementioned GPRC5D-related AEs has also been included for teclistamab (where reported) alongside that of talquetamab in the subsequent sections.

Dysgeusia and weight loss

Dysgeusia and weight loss AESIs are expected for a GPRC5D-targeting drug such as talquetamab, as GPRC5D expression is found in some cells in the oral cavity, which can result in changes in taste, and subsequent weight loss when patients do not want to eat.[182] A summary of the treatment-emergent dysgeusia events for talquetamab and teclistamab is presented in Table 44, and a summary of weight loss in the same population is presented in Table 45.

This data shows that despite 72.1% of patients receiving talquetamab experiencing dysgeusia, this only led to [redacted]%, [redacted]% and [redacted]% of patients having their talquetamab dose discontinued, modified and reduced, respectively.[46] Similarly, weight loss did not lead to many dose discontinuations, modifications or reductions ([redacted]%, [redacted]% and [redacted]% of patients respectively).[46]

Moreover, there were [redacted] fatal outcomes associated with dysgeusia and weight loss events.[46] When considered alongside the low rates of drug discontinuation, modification or reduction, this highlights the potential for weight loss and oral toxicity to be managed with the right supportive care measurements in place.[46]

As expected due to the nature of the GPRC5D-related AESIs, a lower proportion of patients receiving teclistamab experienced dysgeusia of any grade [redacted] or weight loss of any grade [redacted].[40]

Table 44: Dysgeusia for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Dysgeusia[a] (any grade)	111 (72.1)	[redacted]
Grade 3/4	0	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[b]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]Including ageusia, dysgeusia, hypogeusia, and taste disorder. [b]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

Table 45: Weight loss for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Weight loss (any grade)	64 (41.6)	[redacted]
Grade 3/4	9 (5.8)	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

Skin disorders

Skin disorder AESIs are expected for a GPRC5D targeting drug such as talquetamab, as GPRC5D expression has been detected in some of the epithelial cells that make up skin.[167] Consequently, talquetamab may affect GPRC5D expression in the skin, and result in skin

disorders. A summary of the treatment-emergent skin disorder events for talquetamab and teclistamab is presented in Table 46.

This shows that **while 73.4%** of patients receiving talquetamab experienced skin disorders of any grade, this resulted in **1 (0.6%)** Grade 3/4 event and [redacted] fatal outcomes.[119] Skin disorders only resulted in talquetamab discontinuation in [redacted]% of patients, a dose modification in [redacted]% of patients and dose reduction in [redacted]% of patients.[46] The low rates of drug discontinuation, dose modification or reduction, with [redacted] of the events leading to fatal outcomes highlight that these skin disorder AESIs are manageable.[46] Similar to dysgeusia and weight loss, as expected a lower proportion of patients receiving teclistamab experienced skin disorders of any grade ([redacted]).[40]

Table 46: Skin disorders for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Skin disorders (any grade)	113 (73.4)[a]	[redacted][b]
Grade 3/4	1 (0.6)	[redacted][b]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[c]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]Reported as "non-rash skin toxicity" in MonumenTAL-1 [b]Reported as "skin and subcutaneous tissue disorders" in MajesTEC-1 which includes 1 Grade3/4 rash event. [c]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

Rash

As with skin disorders, rash AESIs are expected for a GPRC5D targeting drug such as talquetamab, as GPRC5D is expressed by epithelial cells in the skin, which in some patients will result in itching and rashes.[167] A summary of the treatment-emergent rash events for talquetamab and teclistamab is presented in Table 47.

This shows that a minority of patients receiving talquetamab experienced rash of any grade (31.2%), with few patients ([redacted]%) requiring a dose modification.[46, 119] This did not result in dose discontinuation or fatal outcomes for any patients, while it resulted in a dose reduction in [redacted]% of patients.[46] The low rates of dose modification or reduction considered alongside no patients requiring drug discontinuation or having a fatal outcome highlight that this AESI can be suitably managed during talquetamab treatment.[46] Similar to dysgeusia and skin disorders, as expected a lower proportion of patients receiving teclistamab experienced rash of any grade ([redacted]).[40]

Table 47: Rash for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Rash (any grade)	48 (31.2)	[redacted][a]
Grade 3/4	8 (5.2)	[redacted][a]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[b]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]This includes the following events: rash, rash maculopapular, rash pruritic and erythema. [b]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40] Rasche *et al.* 2025.[119]

Nail disorders

Nail disorders AESIs are expected for a GPRC5D targeting drug such as talquetamab, as GPRC5D expression is expected to occur in the nailbed in humans.[167] Talquetamab may therefore affect the keratin production in these cells, resulting in nail disorder AEs. A summary of the treatment-emergent nail disorder events for talquetamab in Cohort C is presented in Table 48. Data for teclistamab was not included in a side-by-side comparison given that only [redacted] patient in MajesTEC-1 experienced a nail disorder (ingrowing nail).[40]

This shows that roughly half of the patients experienced nail disorders of any grade (54.5%), and this did not result in dose continuation or fatal outcome for any patients, while it resulted in a dose reduction in [redacted]% of patients.[46, 119] The low rates of dose modification or reduction and no patients requiring drug consideration or having a fatal outcome highlight the manageable nature of this AESI.[46]

Table 48: Nail disorders for talquetamab MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)]

AESIs, N (%)	Cohort C (0.8 mg/kg Q2W) [N=154]
Nail disorders (any grade)	84 (54.5)
Grade 3/4	0
Leading to drug discontinuation	[redacted]
Leading to dose modification[a]	[redacted]
Leading to dose reduction	[redacted]
Outcome of fatal	[redacted]

Footnotes: [a] Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Rasche *et al.* 2025.[119]

Infections

Patients with MM are at increased risk of infection.[94] In patients with RRMM, treatment with multiple drugs over time can translate into cumulative immune dysregulation, which compounds the infection risk in a background of existing MM-induced immunosuppression.[33, 89-91] This is of particular concern with BCMA-targeting therapies, which may increase the risk of infection through off-tumour toxicity, the elimination of BCMA-expressing plasma cells and the disruption of BCMA signalling, which further impacts plasma cell survival and proliferation.[33, 89, 91, 183] Consequently, it has been well-established that BCMA-targeting BsAb therapies are associated with higher rates of all-Grade and ≥Grade 3 infections, relative to other non-BCMA MM therapies.[32-36, 38, 39] A summary of the infection events for talquetamab and teclistamab are presented in Table 49.

In MonumenTAL-1, 70.8% of patients in Cohort C receiving talquetamab experienced infections, but the majority of these were low grade, with only [redacted]% of patients experiencing Grade 3/4 infections.[46, 119] [redacted] ([redacted]%) had their talquetamab dose reduced due to an infection and [redacted] ([redacted]%) died due to infections, these were not deemed related to talquetamab by the investigators. Most infections in patients in Cohort C occurred early and improved over time, with [redacted]% of patients having their talquetamab dose modified.

Table 49: Infections for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

AESIs, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Infections (any grade)	109 (70.8)	[redacted]
Grade 3/4	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Footnotes: [a]Dose modification includes delays within cycle, dose reduction and dose skipped.
Abbreviations: AESI: adverse event of special interest; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]

Comparison versus teclistamab

Compared to the low infection rates observed in MonumenTAL-1, a higher proportion of patients receiving teclistamab in MajesTEC-1 had infections. Infections of any grade were reported in [redacted]% of patients receiving teclistamab, with [redacted]% of patients experienced Grade 3/4 infections. Clinicians were required to dose delay or skip more doses to manage the patients as a result of the infection; A higher proportion of dose modifications (dose reduction, dose delay, or dose skip) was observed in MajesTEC-1 than in MonumenTAL-1 ([redacted]% versus [redacted]%).

By targeting GPRC5D, talquetamab may allow for reduced suppression of humoral immunity compared to BCMA-targeting drugs, as BCMA is essential for the humoral immune response. This is widely supported by the literature, including a published study which demonstrated the

lower infection rates (particularly rates of fatal infections) with talquetamab compared to BCMA-targeting T-cell based therapies, and suggested that the potential humoral immunity recovery (evidenced by increased non-clonal IgG levels) with talquetamab is accompanied by rapid and durable responses.[43] Meanwhile, a study investigating the impact of BCMA-targeting BsAb on humoral immunity has shown that there is a significant decrease in polyclonal IgG levels after the start of treatment which showed no recovery over time.[93] The on target off tumour effect of disrupting BCMA and eliminating BCMA expressing plasma cells increases infection risk and diminishes the ability of the immune system to resolve infection.[32-39] This may explain the reduction in the rate of severe infections seen with talquetamab and suggests it may allow for longer term maintenance of immune function compared to BCMA-targeting treatments.[43] Indeed, infection-related mortality was higher in MajesTEC-1, with [redacted] fatal outcomes in MajesTEC-1 compared to [redacted] infection-related deaths in MonumenTAL-1. Patients receiving talquetamab have a lower rate of life-threatening infections and infection-related mortality than those receiving teclistamab, [redacted] This is explored further in Section 2.11.5.

To manage the risk of infections, patients receiving anti-BCMA therapy often receive supportive treatment with IVIg. Talquetamab is expected to reduce the need for supportive IVIg treatment when compared to teclistamab; this is supported by the lower IVIg use observed in patients treated with talquetamab. In MonumenTAL-1, only [redacted]% of patients received IVIg after initiating treatment with talquetamab, compared with [redacted]% in MajesTEC-1.[45, 46]

The reduction in severe infections and associated potential for fatal outcomes may offer significant advantages for patients, addressing a clear concern they noted with BCMA-targeting BsAbs (see Section 1.3.3).[3] Additionally, it could provide broader benefits for the NHS by reducing the demand for IVIg and lessening the healthcare resource burden associated with managing these infections (see Section 3.5.1).

2.11.5 Deaths

A summary of the total number of deaths in MonumenTAL-1 and MajesTEC-1 is presented in Table 50 below. More deaths in MonumenTAL-1 were attributed to progressive disease rather than adverse events. In contrast, a much higher proportion of deaths in MajesTEC-1 were due to adverse events compared to MonumenTAL-1 ([redacted] [[redacted]% of those who died] versus [redacted] [[redacted]% of those who died]).[45, 46] The lower proportion of AE-related deaths observed in MonumenTAL-1 therefore, remains consistent with the overall improved safety profile of talquetamab compared to teclistamab, highlighting that AEs observed with talquetamab remain manageable.

As previously outlined in Section 2.11.4, a higher proportion of infection-related mortality was observed in MajesTEC-1 compared to MonumenTAL-1. Infection-related mortality constitute [redacted]% of patients who died in MajesTEC-1 compared to [redacted]% in MonumenTAL-1, further emphasising the significance of the improved infection safety profile of talquetamab.[45, 46]

Table 50: Summary of total deaths for talquetamab [MonumenTAL-1; Cohort C (0.8 mg/kg Q2W) (September 2024 DCO)] and teclistamab [MajesTEC-1 (August 2023 DCO)]

Death, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]	MajesTEC-1 [N=165]
Total deaths	[redacted] ([redacted]% of all patients)	[redacted] ([redacted]% of all patients)
Deaths due to PD	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died)
Deaths due to AE	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died)
Not study drug related[a]	[redacted] ([redacted]% of those who died or [redacted]% of all AE-related deaths)	[redacted] ([redacted]% of those who died or [redacted]% of all AE-related deaths)
Study drug related[a]	[redacted]	[redacted] ([redacted]% of those who died)
Infection related deaths	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died, or [redacted]% of all AE-related deaths)
Non-infection AE deaths	[redacted] ([redacted]% of those who died)[b]	[redacted] ([redacted]% of those who died)[c]
Other	[redacted] ([redacted]% of those who died)[d]	[redacted] ([redacted]% of those who died)[e]

Footnotes: [a]Related if assessed by the investigator as possibly, probably, or very likely related to study agent [b]Causes of non-infection AE deaths for MonumenTAL-1 Cohort C include the following events: [redacted]. [c]Causes of non-infection AE deaths for MajesTEC-1 include the following events: [redacted]. [d]Other category causes of death for MonumenTAL-1 Cohort C include the following events: [redacted]. [e]Other category causes of death for MajesTEC-1 include the following events: [redacted].

Abbreviations: AE: adverse event; DCO: data cut-off; PD: progressive disease; Q2W: biweekly.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]

2.12 Ongoing studies

The September 2024 DCO is the [redacted] of the MonumenTAL-1 trial, and there are no additional trials planned to further inform the efficacy of talquetamab monotherapy in TCE RRMM patients, or compared to teclistamab. There are other studies which are assessing the efficacy of talquetamab in combination with other therapies, including:

- MonumenTAL-3 (NCT05455320; which is assessing talquetamab in combination with pomalidomide and daratumumab, or talquetamab in combination with daratumumab for the treatment of RRMM patients who have received at least 1 prior line of therapy)[184]
- MonumenTAL-6 (NCT06208150; which is assessing talquetamab in combination with pomalidomide or teclistamab in patients with RRMM who have received 1–4 prior lines of therapy)[185]
- MajesTEC-7 (NCT05552222; which is assessing talquetamab in combination with daratumumab and lenalidomide and teclistamab in combination with daratumumab and lenalidomide in participants with newly diagnosed MM who are either ineligible or not intended for autologous stem cell transplant as initial therapy).[186]

Other exploratory studies assessing the efficacy of talquetamab are also being conducted, including MonumenTAL-2 (NCT05050097), TRIMM-2 (NCT04108195), TRIMM-3 (NCT05338775) and RedirecTT-2 (NCT04586426).[187-191] However, as these studies do not investigate talquetamab as a monotherapy for the treatment of TCE RRMM patients, and therefore, they will not provide evidence that is of relevance to decision making for this submission. Additionally, the TALISMAN safety study (NCT06500884) is ongoing, which aims to further refine the management of talquetamab-related AEs in future clinical practice, but as this is assessing preventative treatments for the oral toxicity associated with talquetamab, the study is not considered to be relevant to decision making.[191]

2.13 Interpretation of clinical effectiveness and safety evidence

Unmet need

Teclistamab represents the only BCMA-targeting therapy routinely commissioned in UK clinical practice and thus currently represents a SoC for TCE RRMM patients in the UK. As a BCMA-targeting BsAb and dexamethasone-free monotherapy, it is the only efficacious and QoL-preserving treatment option for these patients. As such, there are limited alternative treatment options in this setting, thus preventing both patient and clinician choice (which, as outlined in Section 1.3.3, is extremely important in providing patients with an increased sense of control over their disease).[30, 31] Patients consulted by Myeloma UK during the NICE appraisal of teclistamab felt that beyond 4L/5L of therapy, the treatment options become very limited, therefore leading to anxiety and affecting their QoL.[3]

Though teclistamab represented a step-change in the treatment of TCE RRMM patients, RRMM remains a predominantly incurable disease and patients' median life expectancy remains under 24 months.[40] As such, there is a clear need for additional efficacious treatment options for TCE RRMM patients that offers prolonged survival gains while maintaining QoL, allowing them to spend more time with their loved ones.

Additionally, BCMA-targeting BsAbs have a potent redirecting mechanism of action which can impede the ability of the humoral immune system to fight infection, thereby increasing the risk of life threatening infections in patients undergoing treatment.[32-39] This concern has been highlighted noted by patient groups, and the need for IVIg to manage these life-threatening infections places an additional burden on the finite healthcare resources within the NHS.

As outlined in Section 1.3.3, all routinely-commissioned treatments used in the TCE RRMM setting, apart from teclistamab, require concomitant treatment with dexamethasone, which is associated with high levels of toxicity and has a significant impact on the daily lives of patients.[41] Consequently, there is an unmet need for more efficacious dexamethasone-free treatments for TCE RRMM patients that can relieve the symptom burden they currently face.

Attending hospital for treatment can have a substantial psychological impact on patients, who have expressed a desire for a treatment with a flexible dosing regimen that does not require them to attend hospital so frequently, an unmet need that is further supported by clinical opinion.[3, 16] BCMA-targeting BsAbs must be administered weekly for at least the first six months of treatment, so there is a need for additional treatment options for patients that can be administered less frequently and more flexibly so patients can spend less time in hospital. This will subsequently have additional benefits for the NHS as it may result in a reduction in the

healthcare resource burden of treating TCE RRMM patients and also would partially alleviate the burden that transporting patients to hospital has on their carers.

Therefore, there is a significant unmet need for additional efficacious TCE RRMM treatments with distinct targets that are associated with a lower risk of severe infections, as well as a reduced requirement to attend hospital. Such treatments would improve patients' survival, without compromising their QoL and also alleviating the strain on NHS healthcare resources.

Principal findings from the clinical evidence base

Efficacy

The pivotal evidence for talquetamab in this submission is provided by MonumenTAL-1, a three-part Phase I/II, open-label, single-arm study in patients with TCE RRMM.[40, 44] Evidence in this submission is based on Cohort C (0.8 mg/kg Q2W), with data sourced from the [redacted] cut in September 2024 DCO (median follow-up of 31.2 months).[46, 119]

Response and survival outcomes

Patients treated with talquetamab can expect to achieve an impressive response rate, with most patients achieving at least a PR. In MonumenTAL-1, the ORR in Cohort C was 69.5% is one of the highest recorded for MM treatments and is considered to represent the highest magnitude of clinical benefit that can be achieved in orphan disease such as TCE RRMM based on the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies.[119, 150] Treatment with talquetamab was associated with deep responses; as demonstrated by the 40.3% of patients who achieved a ≥CR.[119] Achieving a CR is particularly important for patients with TCE RRMM, as having this level of response following three previous lines of therapy provides a renewed sense of hope that they can expect their remission to last longer and that they are likely to live longer as a result.

These response rates translated to sustained periods of disease remission and survival for patients in MonumenTAL-1. Median PFS was 11.2 months (95% CI, 7.7, 14.6) and approximately [redacted] of patients ([redacted]%, [95% CI, [redacted]) were progression-free after 12 months.[46, 119] As of the September 2024 DCO of MonumenTAL-1, median OS not yet reached (95% CI, NE, NE) after a median follow-up of 31.2 months in Cohort C and 60.8% of patients remained alive after 3 years (95% CI, 51.5, 68.8), clearly demonstrating the sustained survival talquetamab provides to TCE RRMM patients, and reflecting that it represents a promising and effective treatment option for TCE RRMM patients in UK clinical practice.[119]

In the absence of head-to-head clinical trials comparing the effectiveness of talquetamab to teclistamab, ITCs were conducted between the MonumenTAL-1 and MajesTEC-1 studies. Individual patient-level data were used, and the MajesTEC-1 cohort was reweighted to match the baseline characteristics in MonumenTAL-1 via IPTW in line with the best practices described by NICE in TSD 17.[120] This IPTW method adjusted for all 17 key prognostic variables using ATT weighting; an approach which was deemed highly appropriate by HTA experts consulted for this Company submission. As such, this ITC represents the most appropriate evidence for the comparison of the efficacy of talquetamab and teclistamab and the results are directly applicable to UK clinical practice.

Patients receiving talquetamab had a significantly higher likelihood of experiencing an overall response (RR: [redacted] [95% CI: [redacted]; p=[redacted]) compared to patients receiving teclistamab, as

well as a similar likelihood of achieving a CR compared to teclistamab (RR: [95% CI: p=). The DoR was also comparable for talquetamab and teclistamab (HR: [95% CI: p=), suggesting that both treatments elicit equally deep and durable responses. These ITCs also demonstrated that treatment with talquetamab provides patients with comparable PFS to teclistamab (HR: [95% CI,), with a potential improvement in median PFS of months (versus months).[46]

Meanwhile, a statistically significant and clinically meaningful improvement in OS was observed for patients treated with talquetamab compared with teclistamab (HR: [95% CI, ,), following a two-stage subsequent treatment adjustment to remove the effects of non-routine subsequent treatments. Median OS was months in the ATT-adjusted teclistamab cohort but was in the talquetamab population after similar median follow-up durations of 30.4 months and 31.2 months of median follow-up, respectively.[46] This clearly demonstrates that talquetamab represents the efficacious alternative treatment that patients and clinicians aspire for, that will result in further improvements in prognosis for TCE RRMM patients.

This OS benefit in favour of talquetamab was also consistent across scenario analyses exploring the differences in the subsequent treatment distributions in MonumenTAL-1 and MajesTEC-1. Additionally, the ITC results were consistent across an extensive range of sensitivity analyses including alternative weighting, multivariate regression, propensity score matching and using the combined Cohort A+C (weighted 10:90 as per clinical expert feedback) instead of Cohort C for the comparison. Across these scenarios, OS HRs were all .

While multi-faceted, the consistency of the OS benefit across the various sensitivity analyses demonstrates that it is clinically plausible that the OS benefit may be attributed . These differences likely arise from the

BCMA-targeting BsAb can have off-target effects on patients normal B cells and their precursors, resulting in disruptions to humoral immunity.[32-36, 38, 39] Meanwhile, by sparing mature host B-cells and targeting GPRC5D specifically expressed by MM cells, talquetamab may allow patients to maintain better long-term immune function following treatment.[42, 167]

Safety

Talquetamab, a GPRC5D-targeting BsAb, is well tolerated with predictable AEs similar to those known to other BsAbs (i.e., CRS and ICANS) and manageable GPRC5D-specifc AEs (i.e., dysgeusia, weight loss, skin/nail disorders). When compared with BCMA BsAbs, talquetamab demonstrates an improved infection-related safety profile with reduced severe infection rates and infection-related mortality.

Considering the safety profile as a whole, the most common AEs experienced by patients receiving talquetamab were low grade in severity and rarely lead to treatment discontinuation,

with only [redacted]% of patients in Cohort C experiencing a TEAE that led to discontinuation of talquetamab.[46] Talquetamab was associated with similar incidence of BsAb-specific AEs (i.e., CRS and ICANS) as teclistamab; in MajesTEC-1, [redacted]% and [redacted]% of patients experienced CRS (any grade) and ICANS (any grade), respectively, compared to 75.3% and [redacted]% in MonumenTAL-1.[46, 119] Clinicians are already familiar with management strategies of such AEs associated with BsAbs, with appropriate measures already in place in centres which administer other BsAbs or are well-equipped to manage these AEs associated with treatment like CAR T therapy in other indications.

Although GPRC5D is a novel target in the MM treatment landscape, the GPRC5D-related AEs associated with talquetamab due to off-target effects are manageable. These AESIs include dysgeusia, weight loss, skin disorders, rash and nail disorders. In MonumenTAL-1, majority of these AESIs are less than Grade 3/4 although it is acknowledged that the grading criteria for taste-related and nail related AEs do not exceed Grade 2. Nevertheless, the low rates of dose discontinuations (<[redacted]% for each of the forementioned GPRC5D-related AEs) and reductions, and no fatal outcomes due to AESIs highlight that talquetamab has the potential to be well managed with the right supportive care measurements in place.[46]

Consistent with the literature suggesting that BCMA-targeting therapies can impeded the ability of the immune system to fight infection,[32-39] the Grade 3/4 infection rate with talquetamab ([redacted]%) was also lower than that of BCMA-targeting BsAbs ([redacted]%).[40, 46] These benefits translated to less infection-related mortality observed in MonumenTAL-1 ([redacted] patients [[redacted]%]) compared to MajesTEC-1 ([redacted] patients [[redacted]%]). Therefore, highlighting that if reimbursed, talquetamab will meet the unmet need for efficacious alternative treatments for TCE RRMM patients with a reduced risk for severe infection.

Patients consulted by Myeloma UK during TA1015 expressed the importance of providing treatments with reduced infection rates.[3]

"*For me the social isolation due to the increased risk of infection has had the biggest impact. I don't go to crowded places. Even my family have to be really careful.*"

This highlights the QoL benefits that talquetamab could additionally provide through having a reduced severe infection rate compared to current treatments.

The reduction in the severe infection rate with talquetamab would likely translate into a reduced need for patients to receive IVIg to mitigate their infections. As discussed in Section 2.11.3, IVIg, for which there is currently a tight supply of in the NHS,[192] has a high resource burden, and is inconvenient for patients to receive.[95] Consequently, when compared to other BCMA-targeting therapies, talquetamab, a GPRC5D-targeting BsAb, is anticipated to reduce the resource burden on the NHS for the administration of IVIg while additionally alleviating both patients' anxiety about infection (via the reduced rate of life threatening infections) and the inconvenience associated with hospital visits to receive IVIg or manage AEs.

In addition to the favourable infection-related safety profile, talquetamab is also a dexamethasone-free regimen. As a monotherapy, talquetamab can provide patients with an additional dexamethasone-free treatment option in addition to teclistamab, thereby avoiding the burden that treatment regimens including dexamethasone have on patients and not compromising on the improvements in QoL that teclistamab provides.

Strengths and limitations of the clinical evidence base

MonumenTAL-1 was carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), alongside applicable regulatory and country-specific requirements. Measures to ensure data accuracy and reliability included selecting qualified investigators and suitable study sites, reviewing protocol procedures with investigators and study-site staff prior to the study, conducting periodic monitoring visits by the sponsor, and, where applicable, directly transmitting clinical laboratory data from a central laboratory into the sponsor's database. Written instructions were given for the collection, handling, storage, and shipment of samples.[44, 140]

Due to the single-arm design of the MonumenTAL-1 trial, no comparative evidence was available between talquetamab and teclistamab. However, a thorough and robust approach to the ITC was taken by the Company to compare teclistamab and talquetamab, as evidenced by the following:

- The Company were the sponsor of both MonumenTAL-1 and MajesTEC-1 and therefore had access to the IPD for both studies, allowing a robust approach to the trial-vs-trial ITC using IPTW weighting
- To make the two cohorts comparable, it was also possible to adjust for all 17 covariates identified as relevant by UK clinical experts. As MonumenTAL-1 and MajesTEC-1 were designed to include the same patient populations, there was a high degree of overlap between the two trial populations before any adjustment, and following the ATT matching process, the cohorts were well-matched with respect to all of these covariates
- In light of the aforementioned points, HTA experts consulted by the Company reinforced that the ITC analyses presented were methodologically robust and appropriate for comparing talquetamab and teclistamab

MonumenTAL-1 and MajesTEC-1 are both international, multicentre clinical trials, which raises the question of the generalisability of the trial data to the UK context. UK haematology consultants who were specialised in MM confirmed that the baseline demographics and disease characteristics of patients in MonumenTAL-1 were comparable to the patients anticipated to be eligible for talquetamab within the NHS. Therefore, since MajesTEC-1 was recognised as an acceptable data source in the recent NICE appraisal of teclistamab [TA1015], the trial-based indirect evidence on the clinical effectiveness of talquetamab in TCE RRMM is expected to be generalisable to the UK setting and valuable for decision-making.

Summary

The introduction of talquetamab into the UK RRMM clinical pathway would address the unmet need for efficacious treatment options for TCE RRMM patients. It offers an alternative mechanism of action that is associated with a reduction in the risk of severe infections. This more favourable infection-related safety profile will also decrease the requirement for IVIg and the resource burden this has on the NHS. By targeting GPRC5D, talquetamab may allow for reduced suppression of humoral immunity compared to BCMA-targeting drugs, the benefits of which can be observed via the lower Grade 3/4 infection rate associated with talquetamab in MonumenTAL-1 compared to teclistamab in MajesTEC-1. Whilst targeting GPRC5D resulted in off-target effects in patients such as dysgeusia, skin or nail disorders, these GPRC5D-specific AEs remain generally manageable with few drug discontinuations or reductions and no fatal outcomes. As a result, talquetamab is expected to have a reduced healthcare resource requirement associated with the management of infection AEs.[45, 46]

Talquetamab will also have healthcare resource benefits over BCMA-targeting therapies owing to its flexible dosing regimen. As outlined in Section 1.2, patients can receive talquetamab biweekly from the outset of treatment, whereas for BCMA-targeting BsAbs, patients must attend hospital weekly for approximately the first year of treatment.[40, 44] This will therefore reduce frequency of outpatient hospital visits, improving convenience and reducing the associated resource requirements of talquetamab compared to teclistamab. On top of this, talquetamab, like teclistamab, is a dexamethasone free-regimen that could provide patients with improvements in QoL compared to other combination therapies.

The results of the ITC comparing talquetamab and teclistamab show that talquetamab elicits statistically significant and clinically meaningful improvements in OS, with a [redacted]% reduction in the risk of death over time. Talquetamab would have met the previous NICE end-of-life criteria as a treatment for conditions with an average survival of less than 24 months (as is the case still with TCE RRMM) and an improvement in OS of at least 3 months.[193] The median OS for talquetamab was not reached after 31.2 months median follow-up, and over 60% of patients receiving talquetamab remain alive even after 3 years, indicating that the median OS is substantially increased compared to teclistamab with a median OS of [redacted] months (after IPTW ATT weighting).[119] Talquetamab therefore represents an efficacious treatment option for TCE RRMM patients, that will provide them with choice for an alternative treatment that builds upon on the improvements in prognosis initiated with teclistamab.

3 Cost effectiveness

Summary of Cost-Effectiveness Model

- A cost-utility model was developed to estimate the cost-effectiveness of talquetamab versus teclistamab for the treatment of TCE RRMM patients after at least three prior lines of therapy from a UK NHS and Personal Social Services (PSS) perspective.
- Similar to previous, accepted models in NICE evaluations for MM therapies, including the recent NICE appraisal for teclistamab [TA1015],[194] the model was a partitioned survival model consisting of three mutually exclusive health states: (i) pre-progression (PF), (ii) post-progression (PD), and (iii) death.
- The baseline characteristics of patients in the model were based on the Cohort C of the MonumenTAL-1 trial (September 2024 DCO), in line with the primary clinical evidence in this submission.[46]

Base Case Extrapolations: OS, PFS and TTD

- Long-term extrapolations of OS, PFS and TTD for teclistamab were based on the IPD from MajesTEC-1 adjusted to match the MonumenTAL-1 trial. Calibrated LogNormal extrapolations of OS (two-staged adjusted for subsequent treatment), PFS and TTD were used to model long-term survival estimates for teclistamab, in line with the accepted approach in TA1015.[194]
- The PH assumption between talquetamab and teclistamab was assessed across OS, PFS and TTD; it was established that the assumption held for all three endpoints. Consequently, long-term extrapolations of OS, PFS and TTD for talquetamab were derived by applying HRs from the base case ITCs of talquetamab versus teclistamab to the teclistamab reference curves (calibrated LogNormal [two-staged adjusted] OS, PFS, TTD curves, respectively). For OS, the KM data were adjusted to reflect (anticipated) UK clinical practice in the intervention and comparator arms by removing the effects of subsequent treatments not currently available in the UK, via a two-stage adjustment approach.

Model Inputs

- AEs were modelled based on the MonumenTAL-1 for talquetamab and the MajesTEC-1 trial for teclistamab (Grade ≥3 TEAE with ≥5% prevalence)
- In the base case economic analysis, equal health state utility values (HSUVs) were assumed for both talquetamab and teclistamab, derived from MonumenTAL-1 data. Treatment-independent HSUVs were considered appropriate given that both talquetamab and teclistamab are dexamethasone-free T-cell engaging BsAbs, and thus are expected to have a similar impact on patients QoL. Noting the difference in safety profile of talquetamab and teclistamab, AE disutilities were therefore applied to consider the treatment-specific impact of AEs on QoL.
- Cost inputs used in the model (administration, drug acquisition, AEs, monitoring costs, concomitant medication and end-of-life costs) are fully aligned with the accepted inputs used in prior evaluations in MM, in particular, with those used in the NICE appraisal for teclistamab [TA1015], where appropriate.[194-197]
- Subsequent treatments were modelled in line with data from the MonumenTAL-1 and MajesTEC-1 trials, adjusted to account for treatments that are not routinely used in UK clinical practice.[45, 46]

Summary of cost-effectiveness results

- Overall, both the deterministic and probabilistic base case ICERs (£29,277/quality adjusted life years [QALY] and £29,246/QALY, respectively, including PAS discounts) for the comparison of talquetamab and teclistamab demonstrated talquetamab to be a cost-effective use of NHS resource at a willingness-to-pay (WTP) threshold of £30,000 per QALY gain.

- Additionally, talquetamab was associated with positive incremental life years gained (LYGs; 3.22 LYG and 3.29 LYG for the deterministic and probabilistic base case analyses, respectively) and QALYs ([redacted] and [redacted] for the deterministic and probabilistic analyses, respectively) versus teclistamab. These results underline that talquetamab represents an additional efficacious alternative treatment option, and highlight the improvements in both quality and length of life that talquetamab may offer to patients in this setting who are ultimately nearing the end of their terminal illness.
- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrated that the base case cost-effectiveness results were generally robust to an extensive number of sensitivity analyses.
- To address sources of uncertainty in the model, scenario analyses were conducted. These analyses demonstrated that the base case cost-effectiveness conclusions remained unchanged; with talquetamab remaining cost-effective versus teclistamab at a WTP threshold of ~£30,000 per QALY across all scenario analyses. In fact, scenario analyses modelling individually fitted curves to talquetamab PFS, OS and TTD demonstrate that the base case cost-effectiveness analysis may be conservative, with three plausible scenarios resulting in notable decreases to the ICER when compared to the base case.
- Overall, these economic results demonstrate that talquetamab has the potential to address the significant unmet need for an alternative efficacious treatment option with a distinct mechanism of action for TCE RRMM patients, that will build upon improvements in prognosis; ultimately extending and improving the lives of patients, whilst representing a cost-effective use of NHS resource.
- Importantly, the economic results do not fully capture certain key benefits associated with talquetamab that cannot be accounted for in the QALY calculations, including the value of patient/clinician choice and hope associated with providing an additional treatment option for TCE RRMM patients, the reduced anxiety around contracting infections, and the reduction in caregiver burden, which all mean that the base case results likely represent a conservative estimate of the true cost-effectiveness of talquetamab in UK clinical practice.

3.1 Published cost-effectiveness studies

SLRs were conducted to identify published economic evaluations of interventions for patients with TCE RRMM, evidence relating to the HRQoL and utility (humanistic burden) and cost/resource use (economic burden) that may be of relevance to this submission. Full details of all SLRs (including identified HRQoL and cost/resource use studies) are presented in Appendix E, F and G.

An economic SLR was conducted in December 2024 to identify economic evaluations in all patients with RRMM.

Following de-duplication of results, a total of 1,515 records across all searches were screened at the title and abstract stage, of which 168 records were reviewed at the full-text stage. After exclusion of records not meeting the eligibility criteria, 134 records were included from the electronic database searches. A further 105 records were included from the supplementary hand-searches. In total, 239 records were eligible for inclusion, but 226 were deprioritised as they were not relevant to the submission decision problem (not reporting on talquetamab or teclistamab). Eventually, 13 records (reporting on 11 unique studies) were considered for inclusion in the economic SLR. However, of these 13 records, none were considered relevant for

the purpose of this appraisal as they did not contain an economic evaluation comparing talquetamab to teclistamab from a UK perspective.

Full details of the SLR methodology used to identify the economic evaluations relevant to this submission, is provided in Appendix E.

3.2 Economic analysis

As outlined above, no relevant economic evaluations comparing talquetamab to teclistamab from a UK perspective were identified in the SLR. As such, a *de novo* cost utility analysis was conducted for the purpose of this evaluation. This model is described in detail below.

The aim of the economic analysis was to determine the cost-effectiveness of talquetamab versus teclistamab for treating RRMM after at least 3 prior therapies. The analysis was conducted from the perspective of the NHS and PSS, taking into account direct costs and benefits only.

The economic evaluation was approached as follows, in line with the NICE reference case:

- Health outcomes were measured in terms of both LYG and QALYs
- The primary outcome measure for the economic evaluation was the incremental cost effectiveness ratio (ICER; cost per QALY gained) for the comparison of talquetamab versus teclistamab
- Clinical effectiveness for talquetamab and teclistamab was measured through OS and PFS outcomes (see Section 3.3)
- All relevant costs were considered including treatment acquisition costs, administration costs, AEs costs, costs associated with concomitant and subsequent treatments, resource use and end-of-life costs (Section 3.5)
- The model used a lifetime time horizon (equivalent to 40 years). The discount rate was set to 3.5% for both costs and benefits.

3.2.1 Patient population

The population of interest was adult patients with relapsed/refractory multiple myeloma who have received at least three prior therapies, including an IMiD, PI and anti-CD38 mAb and have demonstrated disease progression on their last therapy (Section 1.1). This is aligned with the decision problem for this submission, the licensed indication for talquetamab in the UK and the patients enrolled in the MonumenTAL-1 trial (Section 2.3).

The characteristics of patients entering the model were based on the baseline characteristics of patients in Cohort C of the MonumenTAL-1 trial reported in the latest DCO. As detailed in Section 2.3.1, Cohort C is anticipated to be the cohort of most relevance to UK clinical practice.

Age and sex were included in the model to determine general population mortality and utility inputs. Additionally, mean body weight and body surface area (BSA) were included in the model to calculate drug acquisition costs (Section 3.5.1).

A summary of the patient baseline characteristics used in the economic model are presented in Table 51.

Table 51: Summary of baseline characteristics used in the economic model

Characteristics	TCE RRMM population	Source
Mean age, years	[redacted]	MonumenTAL-1 Cohort C (September 2024 DCO)[46]; Chari *et al.* 2025.[117]
Proportion of female patients, %	41.6	
Mean body weight, kg	[redacted]	
Mean BSA, m^2	[redacted]	

Abbreviations: BSA: body surface area; DCO: data cut-off.

3.2.2 Model structure

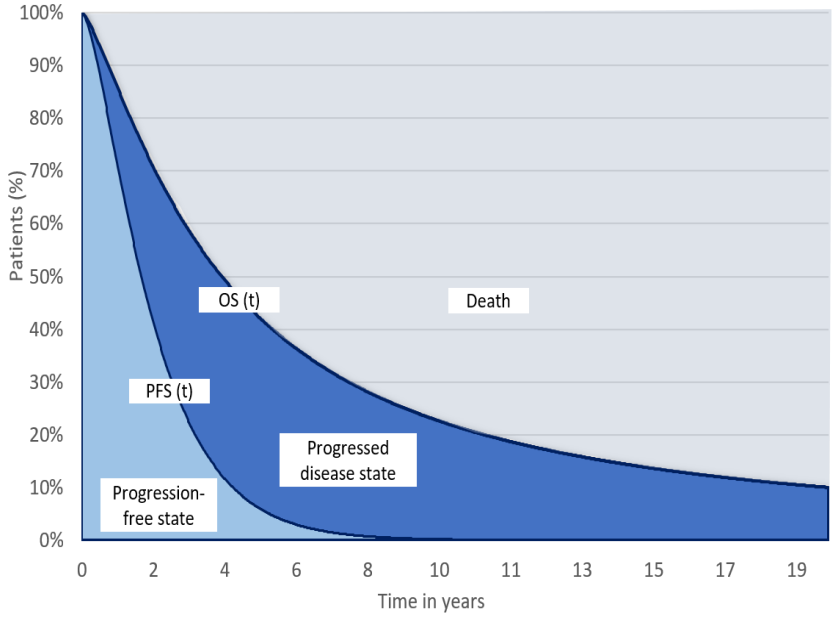
The *de novo* model consisted of three mutually exclusive health states: (i) pre-progression, (ii) post-progression, and (iii) death. In the base case analysis, the occupancy of health states over time was derived from extrapolation of data from the MajesTEC-1 trial for teclistamab (adjusted for population imbalances via the IPTW method using ATT weights as detailed in Section 2.10) and applying HRs to these extrapolations for the Cohort C of the MonumenTAL-1 trial to derive long-term extrapolations for talquetamab (Section 3.3). The proportion of patients occupying each health state was calculated using the PFS and OS survival extrapolations, as described below and as shown in Figure 25:

- The proportion of patients occupying the pre-progression state was calculated as the proportion alive and progression-free (based on PFS extrapolations)
- The proportion of patients occupying the post-progression state was calculated as the proportion alive (based on OS extrapolations) minus the proportion of patients alive and progression-free (based on PFS extrapolations)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS extrapolations)

Patients may have discontinued talquetamab or teclistamab for reasons other than disease progression. As such, TTD was used to determine the time on treatment (ToT) for patients who discontinued treatment before progression. This allowed for the specific health-state costs, such as treatment acquisition, treatment administration and monitoring costs, to be applied appropriately while patients are on or off treatment, while also allowing patients to occupy the pre-progression and post-progression health-states, regardless of whether they are on treatment.

In alignment with the economic model developed during the NICE appraisal for teclistamab [TA1015] and numerous other previous MM NICE submissions, the model used a cycle duration of one week in order to allow granular modelling of treatment costs.[5, 6, 8, 194, 198-204] A half cycle correction was applied in line with modelling best practice and TA1015, to avoid systemic over or underestimation of costs and outcomes.[194, 205]

Figure 25: Partitioned survival model structure



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

Justification for choice of model structure

As with the NICE appraisal for teclistamab [TA1015], a partitioned survival model (PSM) was deemed the most appropriate model structure to inform the cost-effectiveness of talquetamab, as the modelled health states are considered to accurately reflect the natural disease course for patients with TCE RRMM.[194] The key outcomes in this setting, PFS and OS, are time-to-event endpoints. The PSM approach facilitates the direct and intuitive replication of observed data from the MonumenTAL-1 and MajesTEC-1 trials within the economic model, ensuring a precise representation of disease progression and the survival outcomes for patients treated with talquetamab or teclistamab.

As discussed in Section 2.6, the median follow-up in Cohort C of MonumenTAL-1 (September 2024 DCO) was 31.2 months.[119] The PSM structure allows uncertainty in long-term extrapolations to be explored through scenario analyses (see Section 3.11.3).

In alignment with the model developed during the appraisal of teclistamab (TA1015), the progressive and predominantly incurable nature of RRMM means that there is no requirement for a functionality to move backwards between the health states, thus further supporting the use of a PSM for the cost-effectiveness analysis.[194] Additionally, the model structure choice aligns with the extensive precedent for using and accepting PSMs in previous NICE appraisals.[5, 6, 8, 194, 198-204]

As PFS and OS outcomes are modelled independently in the PSM, the lack of an explicit link between these outcomes is a potential limitation of the PSM structure. This may lead to incongruent relationships of PFS and OS (e.g. the curves crossing). However, as PFS is capped by OS in this model, such logical inconsistencies are prevented. Hence, the PSM is considered appropriate to model the occupancy of the pre-progression, post-progression and death health states.

Features of the economic analysis

The NICE evaluation for teclistamab was considered most relevant for this appraisal as the only routinely commissioned 4L+ treatment in the indication of interest (i.e., adult patients with TCE RRMM after three prior lines of therapies who have demonstrated disease progression on the last treatment), and relevant comparator to talquetamab.[194] A summary of the key features of the economic analysis for talquetamab compared with TA1015 is presented below in Table 52.

Table 52: Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	Values accepted in TA1015 (Teclistamab)[194]	Chosen values for current CEM	Justification for talquetamab values
Model structure	Three-state PSM	Three-state PSM	A partitioned survival model accurately reflects disease progression and the observed survival profile of patients with TCE RRMM treated with talquetamab or teclistamab, and is in line with extensive precedent in previous NICE appraisals in RRMM.[5, 6, 8, 194, 198-204]
Time horizon	Lifetime (40 years)	Lifetime (40 years)	A time horizon of 40 years was deemed sufficient to cover the remaining lifetime of patients in the model based on patient starting age of [redacted] years, and is therefore considered sufficient to capture any differences in costs or outcomes between the technologies being compared; the use of 40-year time horizon is aligned with TA1015.[194]
Cycle length	One week	One week	A short cycle duration of one week allows granular modelling of treatment costs; the use of a one week cycle duration is aligned with previous NICE submissions in RRMM (TA338/427[203], TA510[198]/TA783[200] and TA505[204]/TA870[202], TA897[199] and TA1015[194]).
Half cycle correction	Applied	Applied	Half cycle correction was included in the economic model. To reduce systemic over/underestimation of costs and other outcomes, in line with the recommended best practice[205]
Source of utilities	• Treatment-dependent health state utility values (HSUV) for the pre-progression and post-progression health states were utilised. • Pre-progression and post-progression health state utility values for teclistamab were derived from EQ-5D-5L data from	• Treatment-independent HSUVs for the pre-progression and post-progression health states were utilised • Pre-progression and post-progression HSUVs for talquetamab were derived from EQ-5D-	• In TA1015, treatment-dependent HSUVs were deemed appropriate and formed part of the Committee preferred assumptions based on the fact that teclistamab is a dexamethasone-free regimen, while PomDex is a dexamethasone-based regimen; dexamethasone-based treatments are associated with considerable decrements in patient HRQoL.[194] • Given that talquetamab and teclistamab are both BsAbs and dexamethasone-free regimens, it was deemed appropriate to assume equal utilities for both talquetamab

	the MajesTEC-1 trial, cross-walked to EQ-5D-3L based on Hernandez-Alava et al. (2017) dataset (Hernández Alava et al. 2020)[206-208] • Health state utility values (HSUVs) were age-adjusted over the modelled time horizon in line with UK population-norm values for EQ-5D as reported in the HSE 2014 dataset by NICE DSU[209]	5L data from the MonumenTAL-1 trial, cross-walked to EQ-5D-3L based on Hernandez-Alava et al. (2017) dataset (Hernández Alava et al. 2020)[206-208] • HSUVs were age-adjusted over the modelled time horizon in line with UK population-norm values for EQ-5D as reported in the HSE 2014 dataset by NICE DSU[209] Further details can be found in Section 3.4.5.	and teclistamab. AE disutilities were applied to consider the treatment-specific impact of AEs on QoL. • HSUVs were derived from the EQ-5D-5L data from MonumenTAL-1, and informed the HSUVs for both talquetamab and teclistamab. These utility values were deemed to be the most appropriate for use in the cost-effectiveness model, as per the NICE reference case.[210] A scenario analysis using HSUVs derived from the EQ-5D-5L data from MajesTEC-1 is presented in Section 3.11.3.
Source of costs	Costs were based on established sources of costs including the BNF, PSSRU and NHS Reference costs, and included: • Drug acquisition and administration costs • Monitoring costs • Management of AEs (grade 3 and above, with incidence ≥5% in any treatment arm) • Subsequent therapy costs • Concomitant medications • End-of-life costs	Costs were based on established sources of costs including the BNF, PSSRU and NHS Reference costs, and included: • Drug acquisition and administration costs • Monitoring costs • Management of AEs (grade 3 and above, with incidence ≥5% in any treatment arm) • Subsequent therapy costs	Costs are based on established sources of current costs within the NHS and are aligned with previous evaluations in MM[195-197]

		• Concomitant medications • End-of-life costs	

Abbreviations: AE: adverse events; BNF: British National Formulary; EQ-5D-5L: EuroQol-5D, 5 levels; HSUV: health state utility values; MM: multiple myeloma; NHS: National Health Service; OS: overall survival; PFS: progression-free survival; RRMM: relapsed/refractory multiple myeloma.

3.2.3 Intervention technology and comparators

Talquetamab

The intervention included in the cost-effectiveness model was talquetamab. The economic model assumed that patients on talquetamab receive four step-up doses (0.01, 0.06, 0.4 and 0.8 mg/kg), followed by biweekly administration of a maintenance dose of 0.8 mg/kg, in line with the SmPC for talquetamab.[1] As noted in Section 2.3.1, the biweekly administration of talquetamab was deemed most reflective of the anticipated dosing regimen used in UK clinical practice. Additionally, in the aforementioned RealiTAL real-world evidence study, 88% of patients began talquetamab treatment on the biweekly dosing regimen, with the remaining 12% receiving the QW dosing regimen.[15] The Company acknowledges that the licence for talquetamab also includes weekly administration and has considered this in a scenario analysis, wherein weekly and biweekly dosing regimens have been weighted in accordance with anticipated use in UK clinical practice (namely, 10%:90%, respectively) (see Section 3.11.3). The licence for talquetamab states that treatment should be administered until disease progression or unacceptable toxicity.[1] As such, treatment costs for talquetamab are modelled until the end of the TTD period to align with the recommendations of the SmPC.[1]

Teclistamab

As described in Section 1.1, teclistamab is considered to be the most relevant comparator to talquetamab in this submission The economic model assumed that patients on teclistamab received two step-up doses (0.06 and 0.3 mg/kg), followed by a regimen of weekly administrations (1.5 mg/kg).[211] The model assumed that a proportion of patients switch from QW to Q2W dosing if they have had a CR or better for at least 6 months, in line with the SmPC for teclistamab.[194, 211] As per the Committee's preferred approach in TA1015, the reduced dose frequency of teclistamab was modelled starting from 52 weeks, using a Gompertz distribution curve based on the MajesTEC-1 data (IPTW ATT-weighted) to model the reduced dose frequency at different time points from 52 weeks onwards.[194] The licence for teclistamab states that treatment should be administered until disease progression or unacceptable toxicity. As such, teclistamab treatment costs are modelled until the end of the TTD period to align with the recommendations of the SmPC.[211]

3.2.4 Subsequent treatments

As noted in Section 2.10.4, due to the international nature of MonumenTAL-1 as well as MajesTEC-1, subsequent treatments received in both MonumenTAL-1 and MajesTEC-1 do not fully reflect UK clinical practice.

As outlined in Section 2.10.4, both the MonumenTAL-1 and MajesTEC-1 data were adjusted using a two-stage OS adjustment approach to remove the effects of subsequent treatments which are not routinely available in UK clinical practice. The adjusted proportions for subsequent therapies received by patients in MonumenTAL-1 and MajesTEC-1 have been presented in Table 27 in Section 2.10.4. It was deemed more appropriate to therefore inform the base case with the two-stage OS adjusted data wherein all non-routine UK subsequent treatments had been removed, and treatments available in current UK clinical practice were considered. Scenario analyses with differing assumptions relating to subsequent treatments were also conducted to assess impact on cost-effectiveness estimates (Section 3.11.3).

3.3 Clinical parameters and variables

3.3.1 Survival inputs and assumptions

The economic model is a cohort-based PSM consisting of three mutually exclusive health states: pre-progression, post-progression and death. The proportion of patients in each health state at each weekly model cycle was determined for talquetamab and teclistamab from cumulative survival probabilities from PFS, and OS extrapolations, while a separate TTD extrapolation was used to determine the proportion of patients in the model who remained on treatment. Despite having extensive trial follow-up data, the follow-up periods for MonumenTAL-1 (median follow-up for Cohort C: 31.2 months) and MajesTEC-1 (median follow-up: 30.4 months) were shorter than the model time horizon and extrapolations of OS, PFS and TTD data were required.[119, 212]

Of note, the three modelled endpoints (OS, PFS and TTD) are inherently linked outcomes (see Section 3.3.5) in the context of RRMM, with changes in one of these parameters ultimately resulting in changes to the others. As such, it is important that a generally consistent modelling approach is applied across all three endpoints. Therefore, as detailed in the following sections, in the base case analysis long-term survival outcomes for talquetamab were derived by applying a HR to teclistamab extrapolations, using a consistent approach across all three endpoints.

The population included in the base case analysis corresponded to Cohort C of the MonumenTAL-1 (N=154) for talquetamab and the “All Treated Analysis set” of the MajesTEC-1 trial (N=165) for teclistamab.

3.3.2 Overall survival

Teclistamab

Owing to the recency of the NICE appraisal for teclistamab, the modelling approach for teclistamab in this submission is aligned to the approach that was accepted by the Committee in TA1015.[194] The teclistamab OS extrapolation was therefore derived based on the IPD from MajesTEC-1 adjusted to match the MonumenTAL-1 trial (see Section 2.10.3). As per TA1015, the OS extrapolation for teclistamab informing the base case analysis included the application of GPM cap, two-stage subsequent treatment adjustment (as described in Section 2.10.4) and calibration of OS extrapolation to clinician estimates that were obtained as part of NICE TA1015.[194] The calibrated LogNormal OS extrapolation was accepted in TA1015, and therefore, similarly informs the base case extrapolation of teclistamab in this submission, and is considered to represent the most robust estimate of long-term survival outcomes of teclistamab available.[194] The resulting OS extrapolation for teclistamab is presented in Figure 28, with long-term estimates of OS provided in Table 53.[194]

In line with the approach taken for teclistamab in TA1015, and as described in Section 2.10.4, the use of OS data post-subsequent treatment adjustment was considered the most appropriate evidence to include in the base case analysis.[194] The base case ITC approach detailed in Section 2.10.5 was utilised in the base case economic analysis as this approach best reflects both the anticipated UK clinical practice in the intervention arm (i.e., patients able to receive subsequent teclistamab after talquetamab) and as well as current UK clinical practice in the comparator arm (i.e., patients receiving treatments currently available within the NHS following progression on teclistamab).

Table 53: Overview of survival rates for teclistamab OS extrapolations (including two-stage OS adjustment, with GPM cap)

Survival model	OS survival rates (%)	
	10 years	15 years
Modelled OS extrapolation for teclistamab in TA1015*		
Calibrated LogNormal	10%	3%

Footnotes: *calibrated to clinician estimate of OS at 10- and 15-years.
Abbreviations: NA: not applicable; OS: overall survival; TA: technology appraisal.

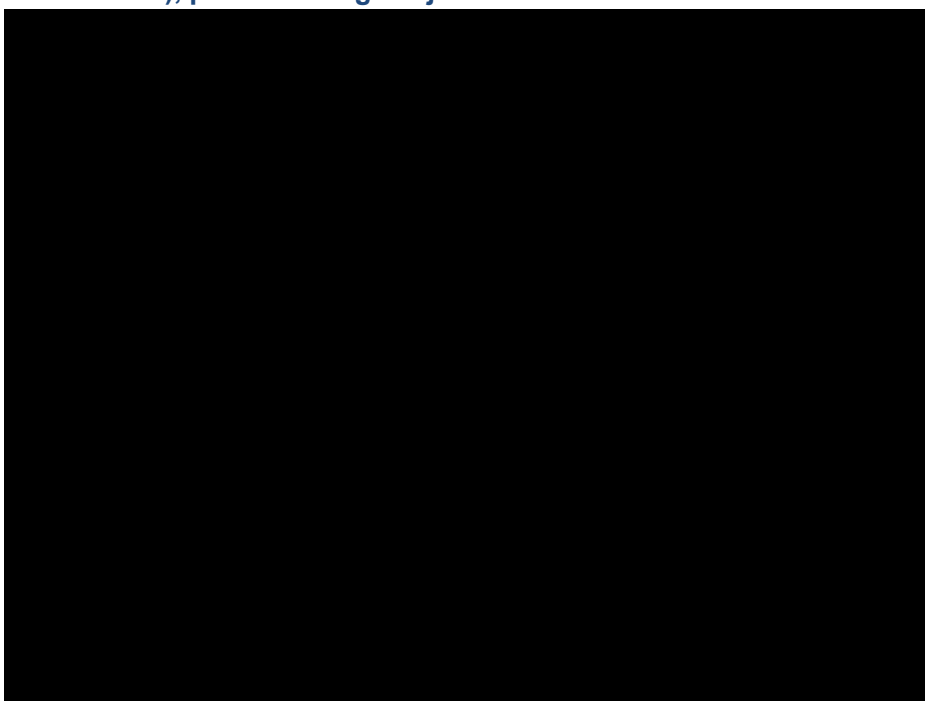
Talquetamab

To determine the most appropriate approach to modelling OS for talquetamab, the PH assumption was first assessed. A log-cumulative hazard plot for talquetamab and teclistamab post two-stage adjustment is presented in Figure 26, and a Schoenfeld residual plot is presented in Figure 27. For OS post-adjustment, the log cumulative plot is predominantly parallel (Figure 26). The Schoenfeld residual plot is horizontal with a p-value >0.05, providing no evidence that the PH assumption should be rejected (Figure 27).

As a result, the use of a HR (post two-stage adjustment) to derive the talquetamab OS extrapolation from the teclistamab extrapolation was considered as the most appropriate and robust approach representing the least uncertainty, particularly as the teclistamab OS extrapolation has recently been reviewed and agreed upon by the NICE committee as part of TA1015.[194] In line with TA1015, the teclistamab calibrated LogNormal curve for OS was selected to act as the reference curve, and talquetamab was modelled by applying the ITC two-stage adjusted OS HR of [redacted] (95% CI: [redacted]; see Section 2.10.5) to the teclistamab extrapolation.[194] This allowed a corresponding OS extrapolation to be derived for talquetamab.

This approach builds on the Committee's preferred assumption for the teclistamab OS extrapolation in TA1015 and also permits the use of the robust (trial versus trial) ITC results, which represent the highest grade of indirect evidence available assessing the relative effects between talquetamab and teclistamab.[194] The resulting OS extrapolation for talquetamab is presented in Figure 28.

Figure 26: Log-cumulative hazard plot OS, talquetamab and teclistamab, ATT (adjusted for 17 variables), post two-stage adjustment



Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; IRC: independent review committee; OS: overall survival.

Figure 27: Schoenfeld residual plot for OS, talquetamab and teclistamab, ATT (adjusted for 17 variables), post two-stage adjustment

Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

Figure 28: Talquetamab and teclistamab OS extrapolation, post two-stage adjustment

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Scenario analyses

As described in Section 2.10.6, two alternative scenario analyses were explored whereby a different approach to including subsequent treatments in MonumenTAL-1 that are not available in UK clinical practice was used; this was done to assess their impact on the base case cost-effectiveness estimates. As noted in Section 2.10.6, the OS HRs across the additional subsequent treatment scenarios show consistency with the base case ITC analysis result (HR: [redacted] [95% CI: [redacted]]), demonstrating that the OS benefit associated with talquetamab is not a result of differences in the subsequent treatment distributions between talquetamab and teclistamab.

- **Scenario 1 ('All-Out'):** In addition to removing subsequent treatments not available in UK clinical practice (as per the base case ITC approach), subsequent use of teclistamab was also removed from MonumenTAL-1. All remaining subsequent treatments from MonumenTAL-1 were reweighted accordingly. The OS HR applied in this 'All-Out' scenario was [redacted] (95 CI: [redacted]).
- **Scenario 2 ('All-In'):** As per the base case ITC approach, OS was adjusted similarly by removing subsequent treatments that are not available in UK clinical practice. However, subsequent use of talquetamab following teclistamab was permitted (as was the subsequent use of teclistamab after talquetamab). All remaining subsequent treatments from MonumenTAL-1 were reweighted accordingly. The OS HR applied in this 'All-In' scenario was [redacted] (95% CI: [redacted])

3.3.3 Progression-free survival

To inform long-term estimates of PFS in the model for talquetamab and teclistamab, it was necessary to extrapolate PFS data through the application of parametric survival functions.

Teclistamab

Similar to the approach taken for OS, the PFS extrapolation for teclistamab informing the base case analysis was derived based on the IPD from MajesTEC-1, following the accepted approach

in TA1015.[194] The PFS extrapolations implemented in the model include a cap to ensure that PFS did not exceed OS for teclistamab, in turn ensuring clinical plausibility of PFS extrapolations. The PFS extrapolation for teclistamab was calibrated after 5 years to clinician estimates of 10- and 15-year PFS. The resulting PFS extrapolation for teclistamab is presented in Figure 31, with long-term estimates of PFS provided in Table 54.

Table 54: Overview of predicted long-term estimates for teclistamab PFS extrapolation

Survival model	Proportion of patients progression free (%)	
	10 years	15 years
Modelled PFS extrapolation for teclistamab in TA1015*		
Calibrated LogNormal	5%	1%

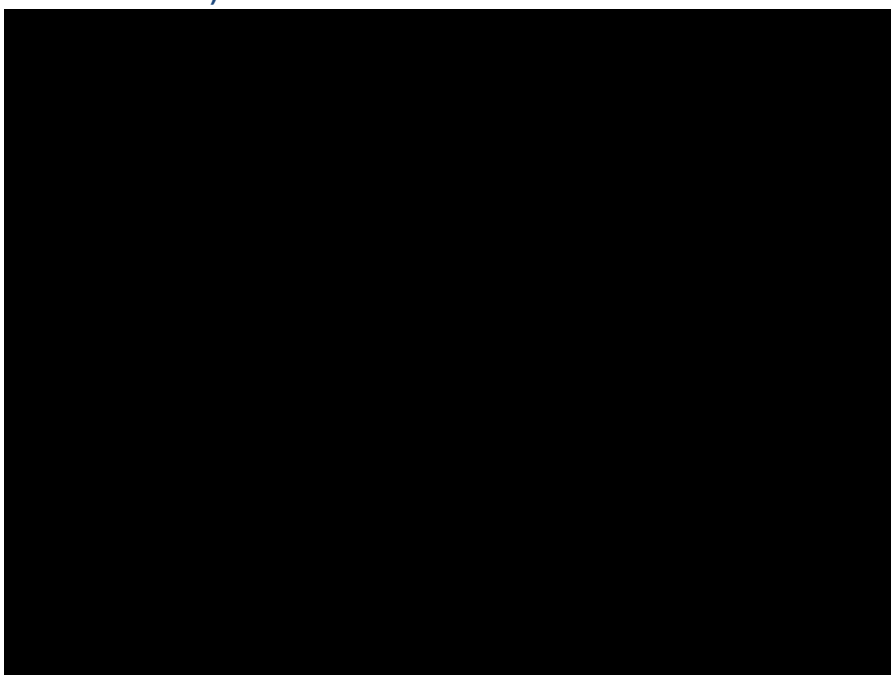
Footnotes: *calibrated to clinician estimate of PFS at 10- and 15-years.
Abbreviations: PFS: progression-free survival; TA: technology appraisal.

Talquetamab

The PH assumption for talquetamab and teclistamab PFS (ATT; adjusted for 17 variables) was assessed. A log-cumulative hazard plot for talquetamab and teclistamab is presented in Figure 29, and a Schoenfeld residual plot is presented in Figure 30. For PFS, the log cumulative plot is predominantly parallel apart from a slight overlap for talquetamab and teclistamab at later timepoints (Figure 29). The Schoenfeld residual plot p-value is >0.05, providing no evidence that the PH assumption should be rejected (Figure 30).

As a result, in line with the approach taken for OS, in the base case economic analysis, the use of a HR to derive PFS for talquetamab from the PFS for teclistamab was considered to represent the most appropriate approach. The teclistamab PFS extrapolation has recently been reviewed and agreed upon by the NICE committee as part of TA1015, therefore, the teclistamab calibrated LogNormal curve for PFS was selected to act as the reference curve, and talquetamab was modelled by applying the PFS ITC HR of [redacted] (95% CI: [redacted]) to the teclistamab extrapolation.[194] This allowed a corresponding PFS extrapolation to be derived for talquetamab. The resulting PFS extrapolation for talquetamab is presented in Figure 31.

Figure 29: Log-cumulative hazard plot PFS, talquetamab and teclistamab, ATT (adjusted for 17 variables)



Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; IRC: independent review committee; PFS: progression-free survival.

Figure 30: Schoenfeld residual plot for PFS, talquetamab and teclistamab, ATT (adjusted for 17 variables)

Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; PFS: progression-free survival.

Figure 31: Talquetamab and teclistamab PFS extrapolation

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

3.3.4 Time to treatment discontinuation

Teclistamab

Similar to the approach taken for OS and PFS, the TTD extrapolation for teclistamab informing the base case analysis was derived based on the IPD from MajesTEC-1, following the accepted approach in TA1015.[194] The TTD extrapolation for teclistamab was calibrated after 5 years to clinician estimates of 10- and 15-year TTD. The resulting TTD extrapolation for teclistamab is presented in Figure 34.

Table 55: Overview of predicted long-term estimates for teclistamab TTD extrapolation

Survival model	Patients on treatment (%)	
	10 years	15 years
Modelled TTD extrapolation for teclistamab in TA1015*		
Calibrated LogNormal	3%	1%

Footnotes: *calibrated to clinician estimate of TTD at 10- and 15-years.
Abbreviations: TA: technology appraisal; TTD: time to treatment discontinuation.

Talquetamab

The PH assumption for talquetamab and teclistamab TTD (ATT; adjusted for 17 variables) was assessed. A log-cumulative hazard plot for talquetamab and teclistamab is presented in Figure 32, and a Schoenfeld residual plot is presented in Figure 33. For TTD, the log cumulative plot shows a parallel across the middle timepoints with some overlap for talquetamab and teclistamab at early and late timepoints (Figure 32). The Schoenfeld residual plot p-value is >0.05, providing no evidence that the PH assumption should be rejected (Figure 33).

Consequently, in the base case economic analysis, the use of a HR was considered to represent the most appropriate approach. As the teclistamab TTD extrapolation has recently been reviewed and agreed upon by the NICE committee as part of TA1015, the teclistamab calibrated LogNormal curve for TTD was selected to act as the reference curve, and talquetamab was modelled by applying the ITC for talquetamab versus teclistamab TTD HR to the teclistamab LogNormal extrapolation.[194]

The ITC described in Section 2.10 comparing talquetamab and teclistamab additionally assessed TTD as an outcome. The results of the comparison showed there was a very similar TTD for both treatments (HR: [redacted] [95% CI: [redacted]]). The HR of [redacted] was therefore applied to the teclistamab curve to allow a corresponding TTD extrapolation to be derived for talquetamab. This approach permits the use of the ITC results, which represent the highest grade of evidence available assessing the relative effects between talquetamab and teclistamab and also builds on the Committee's preferred assumption for the teclistamab TTD extrapolation in TA1015.[194] The resulting TTD extrapolation for talquetamab is presented in Figure 34.

Figure 32: Log-cumulative hazard plot TTD, talquetamab and teclistamab, ATT (adjusted for 17 variables)

Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; IRC: independent review committee; TTD: time to treatment discontinuation.

Figure 33: Schoenfeld residual plot for TTD, talquetamab and teclistamab, ATT (adjusted for 17 variables)

Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 CSR (September 2024 DCO).[46] MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]
Abbreviations: ATT: average treatment effect in the treated; TTD: time to treatment discontinuation.

Figure 34: Talquetamab and teclistamab TTD extrapolation

Abbreviations: KM: Kaplan-Meier; TTD: time to treatment discontinuation.

3.3.5 Summary of survival approaches

An overview of the approaches used to model OS, PFS and TTD for talquetamab and teclistamab in the base case cost-effectiveness analysis are presented in Table 56.

Table 56: Summary of base case survival approaches

	Talquetamab	Teclistamab (as per TA1015)[194]
OS	Derived by applying the two stage-adjusted ITC OS HR	Calibrated LogNormal[a]

	([redacted]) to the teclistamab OS curve	
PFS	Derived by applying the ITC PFS HR ([redacted]) to the teclistamab PFS curve	Calibrated LogNormal[b]
TTD	Derived by applying the ITC TTD HR ([redacted] to the teclistamab TTD curve	Calibrated LogNormal[c]

Footnotes: [a] Aligned to TA1015: Calibrated after 5 years to result in 10-year OS of 10% and 15-year OS of 3% in line with clinicians' consensus on survival estimates; [b] Aligned with TA1015: Calibrated after 5 years to result in 10-year PFS of 5% and 15-year PFS of 1% in line with mean clinicians' survival estimates. [c] Aligned with TA1015: Calibrated after 5 years to result in 10-year TTD of 3% and 15-year TTD of 1% in line with mean clinicians' survival estimates.
Abbreviations: HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Scenario analyses

As described above, a HR approach was adopted to derive the OS (post-subsequent treatment adjustment), PFS and TTD extrapolations for talquetamab from the teclistamab extrapolations. This approach was deemed the most appropriate approach as the teclistamab survival extrapolations were recently reviewed and agreed upon by the NICE committee as part of TA1015 and there is no evidence to suggest that the PH assumption between talquetamab and teclistamab should be rejected.[194] This approach combined to the use of the trial-versus-trial ITC results, which represent the highest grade of indirect evidence available, is a key strength of evidence base to characterise the relative effects between talquetamab and teclistamab. The combination of these factors reduces any uncertainty associated with the long-term survival extrapolations for talquetamab and as such, the HR approach is deemed the most appropriate approach to deriving the OS, PFS and TTD extrapolations for talquetamab.

However, to supplement this base case analysis, three scenario analyses were conducted whereby individually fitted curves were modelled for talquetamab OS, PFS and TTD (Section 3.11.3). Studies have demonstrated that in RRMM OS and PFS are inherently interlinked clinical outcomes, with changes in one of these parameters ultimately resulting in changes to another, which is also acknowledged in NICE TSD19.[213-215] Additionally, as teclistamab and talquetamab are both treat-to-progression treatments, PFS and TTD are also linked. It can therefore be inferred that OS and TTD are also inherently linked. As such, in scenarios using independent extrapolation, it was considered most appropriate to select the same extrapolation curves (and thus curves with the same underlying hazard function) across the three outcomes. This aligns to the approach taken in TA1015 whereby the LogNormal curve was selected for OS, PFS and TTD.[194]

Using LogNormal distribution for OS, PFS and TTD was first explored as a scenario analysis as the LogNormal provided the best statistical fit for PFS and TTD and the second-best statistical fit for talquetamab OS. Of note, the difference in AIC/BIC between the LogNormal and Gompertz curves for the talquetamab OS extrapolations is too small (<1) to conclude that there are any material differences between the two curves and how well they fit the data (see Appendix K). In this scenario, the LogNormal extrapolation is used for all three endpoints for both talquetamab and teclistamab, aligning with guidance in NICE TSD 14,[164] which emphasises that substantial justification would be required to fit different types of parametric models to different treatment arms; this is particularly the case for the comparison of talquetamab and teclistamab, which are both BsAb therapies.

Two further supplementary scenario analyses were conducted using the Gamma and Weibull distributions for OS, PFS and TTD. While the Gamma and Weibull distributions have poorer statistical fit (see Appendix K), they provide lower estimates of talquetamab OS and therefore reflect more conservative curve choices for estimating talquetamab long-term survival. It should be noted that, given talquetamab and teclistamab are both BsAbs therapies, it is unclear whether there is sufficient justification to be using different types of extrapolation for the two treatments

The Gamma and Weibull represent the two curves with the lowest predictions of OS for talquetamab, with the exception of the exponential extrapolation. However, the exponential distribution provides the worst statistical fit to the observed talquetamab OS data, an extremely poor visual fit (as shown in Figure 35), and assumes a constant hazard of death. Given the predominantly incurable nature of MM, the exponential distribution represents a clinically implausible curve and was therefore excluded from consideration for the supplementary scenario analyses.

Figure 35. Survival curves and hazard plot for OS, talquetamab, ATT (n=17) (base case subsequent treatment adjustment)

Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46]
Abbreviations: ATT: average treatment effect for the treated; DCO: data cut-off; OS: overall survival; UK: United Kingdom.

3.3.6 Adverse events

The economic model considers Grade ≥3 treatment-emergent AEs that had occurred in at least 5% of patients for either talquetamab (in MonumenTAL-1) or teclistamab (in MajesTEC-1). The 5% cut-off was selected to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are potentially monitored in a less strict manner compared with a clinical trial setting.

The AE rates included in the economic model are presented in Table 57. The disutilities associated with AEs are presented in Section 3.4.4, and the costs associated with the management of AEs are presented in Section 3.5.3.

Table 57: Summary of Grade ≥3 AEs included in the economic model

AE	Talquetamab	Teclistamab
Anaemia	25.3%	[redacted]
Hypertension	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Infections	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neurotoxicity	[redacted]	[redacted]
Neutropenia	21.4%	[redacted]
Pneumonia	[redacted]	[redacted]
Rash	5.2%	[redacted]
Thrombocytopenia	18.2%	[redacted]
Weight loss	5.8%	[redacted]
Source	MonumenTAL-1 (September 2024 DCO)[46] and Rasche *et al,* 2025.[119]	MajesTEC-1 (August 2023 DCO)[45]

Abbreviations: AE: adverse event; DCO: data cut-off.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

In the MonumenTAL-1 trial, patients in the Phase 2 part of the study completed PRO measures related to their HRQoL, including the EORTC-QLQ-C30, PGIS and the EQ-5D-5L questionnaires.

EQ-5D-5L data were collected at the following time points:

- Baseline (after the patient has provided signed informed consent and before any procedures scheduled for the same day as the PRO assessments were collected)
- Day 1 of every odd cycle during treatment (i.e., Day 1 of Cycles 1, 3, 5, 7, 9, 11 etc.),

- Every 16 weeks (±2 weeks) post initial indication of progressive disease or end of treatment (whichever occurred first)

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

Further details on the HRQoL data collected in MonumenTAL-1 are provided in Section 2.6.8.

3.4.2 Mapping

In accordance with the NICE methods manual regarding the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from MonumenTAL-1 were mapped onto the 3L UK value set using the mapping function developed by Hernández Alava, *et al*. (2017) through the NICE Decision Support Unit (DSU), using the EEPRU dataset (Hernández Alava et al. 2020).[206-208] The resulting utility values for talquetamab derived from the mapping are presented in Section 3.4.5.

3.4.3 Health-related quality-of-life studies

An SLR of humanistic burden was conducted to identify evidence on HRQoL, PROs and utilities in patients with TCE RRMM after at least 3 prior therapies (Appendix F). The HRQoL SLR was conducted in December 2024.

Following removal of duplicates, a total of 621 records across all searches were screened at the title and abstract stage, of which 108 records were reviewed at the full-text stage. After exclusion of records not meeting the eligibility criteria, 108 records were included from the electronic database searches. A further 52 records were included from the supplementary hand-searches. In total, 113 records (reporting on 70 unique studies) were included in the HRQoL SLR.

Of the 112 publications, encompassing 70 unique studies, that met the SLR inclusion criteria, eight studies reported direct utility values for the TCE RRMM population (not including cost-effectiveness analyses or HTA reports). These studies comprised two randomised trials (CC-220-MM-001, KarMMa-3), four non-randomised trials (CARTITUDE-1, HORIZON, KarMMA and MagnetisMM-3), and two observational studies (Connect MM, Ishida 2023). While ED-5D-5L utilities have been collected in the MonumenTAL-1 and MajesTEC-1 trials, only EQ-5D VAS published results were identified for talquetamab and teclistamab in the SLR. Beyond the pivotal trials for teclistamab and talquetamab (i.e. MajesTEC-1 and MonumenTAL-1), the other identified studies investigated treatments which are not available in routine UK clinical practice and therefore were not considered relevant for the economic model. A further seven HTA submissions/cost-effectiveness analyses reported mapped utility values for TCE RRMM. However, as talquetamab and teclistamab represent the main treatments of interest to this submission, the utilities for patients receiving other treatments (i.e. beyond talquetamab or teclistamab) are inherently less relevant, particularly given the availability of utility values from the pivotal trials for both teclistamab and talquetamab in this indication.

3.4.4 Adverse reactions

One-off decrements in utility were applied in the model for the proportion of patients who experienced TEAEs (see Section 3.3.1), based on the duration of AEs informed by the September 2024 DCO of the MonumenTAL-1 trial (Cohort C) as a simplifying assumption. A utility decrement for each AE was applied based on the published literature. To explore any uncertainty associated with applying AE disutilities, a scenario analysis explored the exclusion of AE disutilities, with results presented in Section 3.11.3.

A summary of the AE disutilities included in the base case economic analysis for talquetamab and teclistamab are presented in Table 58.

Table 58: Summary of AE disutilities included in the economic model

Adverse event	Utility decrement	Decrement sources	Duration of AEs (days)
Anaemia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Hypertension	0.0000	TA573 (assume no QoL impact, controlled by medication)[217]	[redacted]
Hypokalaemia	-0.2000	TA510 (based on clinical opinion)[218]	[redacted]
Hypophosphatemia	-0.1500	TA559 (2018)[219]	[redacted]
Infection	-0.1900	TA559 (2018)[219]	[redacted]
Leukopenia	-0.0700	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Lymphopenia	-0.0700	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Neurotoxicity	[redacted]	Assumed to have 0 quality of life	[redacted]
Neutropenia	-0.1500	Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Pneumonia	-0.1900	Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Rash	-0.0325	Nafees 2008[220]	[redacted]
Thrombocytopenia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar 2014)[216]	[redacted]
Weight loss	0.0000	Assumed to have 0 disutility in line with TA898[221]	[redacted]

Abbreviations: AE: adverse event; QALY: quality adjusted life year; TA: technology appraisal.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

For reasons outlined in Table 52, given that talquetamab and teclistamab are both dexamethasone-free regimens, it was deemed appropriate to assume equal utilities (i.e. treatment-independent utilities) for the intervention and comparator. As noted in Section 3.4.4, AE disutilities were applied to consider the treatment-specific impact of AEs on QoL. Utility values for the progression-free (PF) and post-progression (PP) health states were therefore, derived using EQ-5D-5L data in MonumenTAL-1, based on the cross-walk method reported by Hernández Alava et al. (2017) to map EQ-5D-5L dimension scores from the MonumenTAL-1 trial to utilities using the UK EQ-5D-3L value set as described in Section 3.4.2. A scenario analysis which utilised the utility values derived from the EQ-5D-5L data in MajesTEC-1 was also explored. Further details on this scenario can be found in Section 3.11.3.

In the economic model, the HSUVs were age-adjusted over the model time horizon in line with UK population norm values for EQ-5D as reported in the HSE 2014 dataset by NICE DSU.[209] A summary of the HSUVs used in the base case analysis for talquetamab and teclistamab is provided in Table 59. A scenario analysis was also conducted to explore an alternative source of utility data (i.e. EQ-5D data from MajesTEC-1) to inform the HSUVs for both teclistamab and talquetamab (see Section 3.11.3).

Table 59: Summary of health state utility values for talquetamab and teclistamab used in the base case economic analysis

Health state	Utility	SE	Source
PF state	[redacted]	[redacted]	MonumenTAL-1 trial (September 2024 DCO, CS model [lowest AIC])
PP state	[redacted]	[redacted]	

Abbreviations: PF: progression-free; PP: post-progression; SE: standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was also conducted to identify cost and resource use studies associated with TCE RRMM in the UK. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

The health economic analysis was conducted from the perspective of the NHS and PSS in England and as such, only included costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2023–2024, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT) costs were used for cost inputs in the model.

Specifically, the following cost components were considered in the model:

- Drug acquisition costs for interventions and comparators
- Associated drug administration costs
- Monitoring costs for intervention and comparators
- Costs associated with the management of AEs
- Cost of co-medication
- Cost of subsequent treatments
- Cost of supportive care and end-of-life palliative care

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

The drug acquisition costs for talquetamab and teclistamab are presented in Table 60, based on their current list prices and licensed doses.

Dosing regimens for talquetamab and teclistamab are shown in Table 61. Both the drug acquisition costs at list price and incorporating the simple PAS discount for talquetamab and teclistamab are provided.

The model included a proportion of doses/administrations of talquetamab being skipped, based on the MonumenTAL-1 trial data wherein [redacted] of talquetamab doses were skipped. The model also included a proportion of [redacted]% teclistamab doses being skipped, in line with data from the MajesTEC-1 trial and Committee preferred assumptions in TA1015.[212]

Additionally, as detailed in Section 3.2.3, a reduced dose frequency of teclistamab was modelled starting from 52 weeks, using a Gompertz distribution curve based on the MajesTEC-1 data (IPTW ATT-weighted) to model the reduced dose frequency at different time points from 52 weeks onwards.[194 40, 194]

Table 60: Summary of drug costs for talquetamab and teclistamab

Intervention	Pack Size	Strength	Price per pack (£)	PAS Discount	Discounted price per pack	Source
Talquetamab	1	3 mg/1.5 mL solution for injection	£326.41	[redacted]	[redacted]	J&J IM. Data on File
	1	40 mg/1 mL solution for injection	£4,352.00	[redacted]	[redacted]	J&J IM. Data on File
Teclistamab	1	30 mg/3 mL solution for injection	£775.14	[redacted]	[redacted]	J&J IM. Data on File
	1	153 mg/1.7 mL solution for injection	£3,952.78	[redacted]	[redacted]	J&J IM. Data on File

Abbreviations: PAS: Patient Access Scheme.

Table 61: Summary of dosing regimens for front-line treatment included in the model

Treatment	Dosing regimen	Administrations per model cycle	Source/Justification
Talquetamab			
Talquetamab (Step Up Dosing for Q2W regimen)	0.01, 0.06, 0.4 and 0.8 mg/kg in Week 1	4	Talquetamab SmPC[1]
Talquetamab Cohort C (Q2W dosing)	0.8 mg/kg once every two weeks	0.5	Talquetamab SmPC[1]
Teclistamab			
Teclistamab (Step Up Dosing)	0.06 and 0.3 mg/kg in Week 1	2	Teclistamab SmPC[12]
Teclistamab (QW dosing)	1.5 mg/kg once every week	1	Teclistamab SmPC[12]
Teclistamab (Q2W dosing)	1.5 mg/kg once every two weeks	0.5	Teclistamab SmPC[12]

Abbreviations: CR: complete response; QW: once weekly; Q2W: once every two weeks; SmPC: Summary of Product Characteristics.

Drug wastage

Both talquetamab and teclistamab dosages are weight dependent. The model assumes drug wastage of [redacted]% per vial for talquetamab, and 28.8% per vial for teclistamab in line with the Committee preferred approach in TA1015.[194]

The approach to calculating wastage followed a similar approach to that taken in TA1015.[194] However in the absence of NHS data regarding the weight of patients receiving talquetamab in UK clinical practice, the mean and standard deviation of weight from Cohort C of the trial was leveraged, with a normal distribution of weight assumed across the talquetamab weight bands stated in the SmPC.[1] The percentage of patients in each weight band according to the normal distribution was then applied to estimate the percentage of each vial wasted per patient. Further details can be found in Appendix N.

Administration costs

The cost of administration was included for both fourth-line and subsequent therapies (Table 62). As both talquetamab and teclistamab are administered subcutaneously, a cost was applied for each subcutaneous administration of each respective drug.

Additionally, both talquetamab and teclistamab require an initial step-up dosing regimen. Both SmPCs for talquetamab and teclistamab state that patients should remain within the proximity of a healthcare facility and monitored for signs and symptoms daily for 48 hours after administration of all doses within the step-up dosing schedule.[1,12] The economic model therefore assumes that each patient treated with talquetamab stays 7 days in hospital in the first cycle and 1 day in hospital in the second cycle. Similarly, each patient treated with teclistamab was modelled to spend 4 days in hospital in the first weekly cycle and 2 days in hospital in the second weekly cycle,[12] in line with TA1015. These hospitalisation costs, based on the cost of an inpatient stay per day of £769.95, are included in the drug administration costs for both talquetamab and teclistamab. A summary of the length hospitalisation included in the model for talquetamab and teclistamab is presented in Table 63.

Table 62: Summary of drug administration costs in the economic model

Administration	Cost	Source
Complex first IV infusion	£554.23	National Schedule of NHS Costs 2023-24, SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – Weighted average of Daycase and Regular Day/Night admissions[222]
Other IV administration	£250.77	National Schedule of NHS Costs 2023-34, SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle - Outpatient[222]
Each SC administration	£108.90	Cancer Service. National Schedule of NHS Costs 2023-24, N10AF: Specialist Nursing, Cancer Related, Adult, Face to face[222]
Oral drug initiation	£247.13	National Schedule of NHS Costs 2023-24, SB11Z: Deliver Exclusively Oral Chemotherapy - Outpatient[222]
Oral drug subsequent	£0.00	Assumption

Abbreviations: IV: intravenous; NHS: National Health Service; SC: subcutaneous.

Table 63: Summary of hospitalisation for teclistamab step-up dosing regimen

Step-Up Dosing Regimen	Frequency (days)	Source
Talquetamab hospital days		
Week 1	7	Talquetamab SmPC[1]
Week 2	1	
Teclistamab hospital days		
Week 1	4	Teclistamab SmPC[12]
Week 2	2	

Abbreviations: SmPC: summary of product characteristics.

Co-medication

In line with the SmPC for talquetamab and TA1015/SmPC for teclistamab, co-medication was included during step-up dosing schedule, as detailed in Table 64 (at list price).[1, 194] The proportion of patients receiving each co-medication (including pre-medication) for talquetamab and teclistamab is presented in Table 65.

Table 64: Co-medication regimens unit costs

Co-medication (oral)	Units	Strength	Price per pack or unit cost (£)	Dosage per administration	Type of administration	Drug or monitoring cost per admin (£)	Source
Dexamethasone PO 2 mg	28	2.0 mg	1.71	16.0 mg	Oral subsequent	0.49	BNF 2025
Paracetamol (acetaminophen)	100	500.0 mg	0.79	825.0 mg	Oral subsequent	0.02	eMIT 2024
Diphenhydramine	20	25.0 mg	3.87	50.0 mg	Oral subsequent	0.39	MIMS, Nytol

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; MIMS: monthly index of medical specialities.

Table 65: Proportion of patients receiving each co-medication (including pre-medication) for talquetamab and teclistamab

% Patients Receiving Co-Medication	Dexamethasone PO 2 mg	Paracetamol (acetaminophen)	Diphenhydramine	Source
Talquetamab	100%	100%	100%	Talquetamab SmPC[1]
Teclistamab	100%	100%	100%	Teclistamab SmPC[12]

Abbreviations SmPC: summary of product characteristics.

3.5.2 Health-state unit costs and resource use

Monitoring costs

Ongoing monitoring costs were included in the model, with the frequency of monitoring visits and tests dependent on whether a patient is in the pre- or post-progression health state in the economic model (Table 66).

Table 66: Unit costs and frequency of routine follow-up care use by health state

Resource Use	Unit Cost (£)	Frequency per week			Source
		PFS (on Tx)	PFS (off Tx)	Post-progression	
Haematologist visit	204.32	0.23	0.08	0.08	NICE TA427[5]
Full blood count	6.95	0.21	0.21	0.39	
Biochemistry	7.31	0.19	0.19	0.33	
Average weekly cost by health state (£)		49.84	19.19	21.47	Calculation

Abbreviations: PFS: progression-free survival; Tx: treatment.

End-of-life cost

A one-off cost representing the cost of terminal care was applied in the model for the proportion of patients that died in each cycle. In line with the approach taken in TA1015, the end of life cost applied in the model (£13,314.00) was taken from the PSSRU oncology reference costs and accounted for both hospital and social care costs in the last year of life.[194]

3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving talquetamab or teclistamab was included in the model. The unit costs per event were based on NHS reference costs 2023–2024 and are presented in Table 67.

AE unit costs were applied to the proportion of patients experiencing each event in either the talquetamab or teclistamab arms in the model and were applied in the first cycle of the model. The total cost across all events included in the model was £[redacted] for talquetamab and £[redacted] for teclistamab, respectively.

Table 67: Summary of AE costs in the base case economic analysis

AE	Unit cost (£)	Source
Anaemia	1,772.73	National Schedule of NHS Costs 2023-24, SA09: Weighted Average of Non-Elective Admissions[222]
Hypertension	774.04	National Schedule of NHS Costs 2023-24, EB04Z: Weighted Average of Non-Elective Admissions[222]
Hypokalaemia	2,061.89	National Schedule of NHS Costs 2023-24, KC05J - Fluid or Electrolyte Disorders: Weighted Average of Non-Elective Admissions[222]
Hypophosphatemia	2,061.89	Assumed equal to hypokalaemia (per TA658)[201]

Infection	2,528.21	National Schedule of NHS Costs 2023-24, WJ03A-F: Weighted Average of Non-Elective Admissions[222]
Leukopenia	2,058.10	National Schedule of NHS Costs 2023-24, SA08: Weighted Average of Non-Elective Admissions[222]
Lymphopenia	2,058.10	National Schedule of NHS Costs 2023-24, SA08: Weighted Average of Non-Elective Admissions[222]
Neurotoxicity	7,310.00	Assumed equivalent to the cost of three ICU Days. ICU Costs were sourced from NHS Reference Costs 2023-24 (Weighted Average of XC01Z-07Z, Non-Specific Critical Care)[222]
Neutropenia	2,522.56	National Schedule of NHS Costs 2023-24, SA35: Weighted Average of Non-Elective Admissions[222]
Pneumonia	1,367.85	National Schedule of NHS Costs 2023-24, CB02: Weighted Average of Non-Elective Admissions[222]
Rash	511.89	National Schedule of NHS Costs 2023-24, JD07A-K Weighted Average of Non-Elective Short Stays[222]
Thrombocytopenia	2,515.70	National Schedule of NHS Costs 2023-24, SA12: Weighted Average of Non-Elective Admissions[222]
Weight loss	577.91	National Schedule of NHS Costs 2023-24, FD04A-E Weighted Average of Non-Elective Short Stays[222]

Abbreviations: AE: adverse event; ICU: intensive care unit; NHS: National Health Service.

Treatment of infections: Costs associated with Immunoglobin (Ig)

As highlighted in Section 2.11.4 and consistent with the literature, talquetamab has a lower rate of severe infections than BCMA-targeting BsAbs, owing to differences in the mechanism of action. By targeting GPRC5D, talquetamab may result in reduced suppression of humoral immunity compared to BCMA-targeting drugs, as BCMA is essential for the humoral immune response.[43] As a result of the reduction in the severe infection rate with talquetamab, patients will require less of the resource-intensive IVIg to mitigate their infections. As such, the impact of the reduction in IVIg with talquetamab was reflected accordingly in the economic model by modelling the cost associated with IVIg (in addition to the cost associated with the infection itself [see Section 3.5.3]).

A summary of the proportion of patients receiving IVIg in the talquetamab and teclistamab arms and the number of doses received, as modelled in the economic model is provided in Table 68 and detailed below:

- The proportion of patients receiving IVIg in the talquetamab and teclistamab arms is modelled in line with the proportion of patients who received IVIg following commencement of talquetamab and teclistamab in the MonumenTAL-1 ([redacted]%) and MajesTEC-1 ([redacted]%) trials, respectively. The proportion of patients receiving IVIg in the teclistamab arm in the economic model is also in line with the Committee preferred assumption in TA1015. Likewise, the proportion of patients receiving IVIg in the talquetamab arm aligns to consultant haematologist opinion.
- The number of doses of IVIg received was modelled in line with the Committee preferred assumptions in TA1015, namely 9 doses of IVIg and summarised in Table 68.[194]

Drug acquisition costs for IVIg treatment were sourced from the BNF (2025) and are summarised in Table 69. While multiple brands of Ig treatment are available, the cheapest of these brands were chosen based on the assumption that NHS would aim to optimise costs, as a conservative assumption. The dosing of Ig was based on the guidelines set out in the NHS Clinical Commissioning Group Each applied to the mean weight of the population in the cost-effectiveness model.[223] The administration costs of IV infusion were also taken into consideration in line with the values provided in Table 62.

Table 68: IVIg dosing regimen: Base case analysis (Ig usage for any reason, following commencement of teclistamab or talquetamab)

Treatment	Number of doses (as per TA1015)	Proportion of patients (%)	Source
Talquetamab	9	[redacted]	MonumenTAL-1 (Cohort C; September 2024 DCO)[46]
Teclistamab	9	[redacted]	MajesTEC-1 (August 23 DCO)[224]

Abbreviations: DCO: data cut-off; IVIg: intravenous immunoglobulin.

Table 69: IVIg drug acquisition costs

Ig	Units	Strength	Price per pack or unit cost (£)	Dosage per administration	Drug or monitoring cost per administration (£)	Administration cost (£)	Source
Octagam	1	10.0 g	690.00	[redacted]	[redacted]	250.77	BNF 2025

Abbreviations: IVIg: intravenous immunoglobulin.

3.5.4 Miscellaneous unit costs and resource use

Subsequent treatments

Distribution of subsequent treatments

A summary of the proportion of patients receiving subsequent therapies in MonumenTAL-1 (Cohort C) and MajesTEC-1 is presented in Table 26 (Section 2.10.4).

However, as described in Section 2.10.5, in both MonumenTAL-1 and MajesTEC-1 some patients received subsequent treatment regimens which are not routinely available in UK clinical practice. In line with the approach accepted in TA1015,[194] the OS data for both talquetamab (Cohort C) and teclistamab were consequently adjusted using the two-stage approach (described in Section 3.3.2) as per NICE TSD 16 to remove the effects of subsequent treatments not routinely available in the UK.[164] The resulting subsequent treatment distributions used to inform the costs of subsequent treatments following talquetamab and teclistamab in the economic model are presented in Table 70.

Full details of the modelled dosing regimens and associated costs for each subsequent therapy regimen can be found in Appendix I.

Table 70: Summary of the subsequent treatment distributions (re-weighted, to adjust for treatments relevant to UK clinical practice) following either talquetamab or teclistamab in the base case analysis

Subsequent treatment, %	Talquetamab (MonumenTAL-1; Cohort C [a]	Teclistamab (MajesTEC-1 [a]
Bendamustine	[redacted]	[redacted]
Bortezomib + chemo	[redacted]	[redacted]
Cisplatin + chemo	[redacted]	[redacted]
Cyclophosphamide based	[redacted]	[redacted]
Cyclophosphamide + pomalidomide + dexamethasone	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Doxorubicin + vincristine + dexamethasone	[redacted]	[redacted]
Lenalidomide + dexamethasone	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]
Melphalan + dexamethasone	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]
Pomalidomide + dexamethasone	[redacted]	[redacted]
Selinexor + dexamethasone	[redacted]	[redacted]
Teclistamab	[redacted]	[redacted]

Footnotes: [a] Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO);[46] J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[40]

Proportion of patients on subsequent treatment and duration of treatment

Proportion of patients receiving subsequent treatment

The proportion of patients receiving subsequent treatment following progression on talquetamab and teclistamab was based on MonumenTAL-1 and MajesTEC-1, respectively.[40, 46] As such, for the talquetamab arm, [redacted]% of patients were modelled to receive a subsequent therapy following progression on talquetamab, in line with the MonumenTAL-1 trial data (Cohort C; September 2024 DCO).[46] For the teclistamab arm, in line with the MajesTEC-1 trial data and the approach accepted by the Committee in TA1015, [redacted]% of patients were assumed to receive a subsequent therapy following progression on teclistamab.[194, 212]

Duration of subsequent treatment

Patients receiving subsequent therapies (other than teclistamab) following progression on talquetamab or teclistamab were assumed to receive an average of 4 months of subsequent treatment in line with Yong et al. (2016) based on the Committee preference in TA1015.[194, 225] Patients receiving teclistamab as a subsequent treatment are likely to receive treatment for a longer duration compared to the other treatments which are less effective. Therefore, the duration of subsequent treatment with teclistamab was based on MonumenTAL-1 and estimated to be [redacted] (SE: [redacted]) months on average.[46]

Scenario analyses

As detailed in Section 2.7 and Section 3.2.4, owing to the international nature of the clinical trials, some patients in MonumenTAL-1 and MajesTEC-1 received treatments not relevant to UK clinical practice. Consequently, the described adjustment was performed to ensure that the base case ICER most accurately reflects UK clinical practice. This included the removal of talquetamab as a subsequent treatment following teclistamab, in order to reflect current UK clinical practice whereby talquetamab is not yet reimbursed.

Three scenario analyses were conducted to explore these assumptions further in Section 3.11.3,:

- 'All-Out' scenario: To account for any uncertainty associated with BsAbs being included as subsequent treatments in the talquetamab arm but not the teclistamab arm, a scenario analysis was performed in which teclistamab could not be received by patients following treatment with talquetamab (i.e. removal of teclistamab from MonumenTAL-1]). All other treatments in MonumenTAL-1 were reweighted accordingly

- 'All-In' scenario: this exploratory scenario analysis was conducted to illustrate the impact of patients receiving subsequent talquetamab after teclistamab to reflect potential future UK clinical practice once talquetamab is reimbursed. This scenario includes patients receiving both subsequent talquetamab following teclistamab treatment ([redacted]%; mean duration of [redacted] [SE: [redacted] months], based on MajesTEC-1) and subsequent teclistamab following talquetamab treatment . All other treatments in MonumenTAL-1 were reweighted accordingly

- Scenario 3: This additional scenario analysis was conducted to explore the impact of an alternative approach to the distribution of non-teclistamab subsequent therapies, solely based on clinical expert opinion received in TA1015 wherein experts estimated the treatment distribution split for PomDex/PanBorDex/SelDex to be 70%/20%/10%.[194]

3.6 Severity

The severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the absolute and proportional severity modifiers.[226] The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[227] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2018–2020.[228] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava et al. (2022) through the NICE DSU.[229] The baseline characteristics for the modelled population was informed by Cohort C of the

MonumenTAL-1 trial (September 2024 DCO), as this is anticipated to be the population of most relevance to UK clinical practice (as discussed in Section 2.3.3). The total QALYs for the current MM population in the UK were based on the results of the base case economic analysis for talquetamab (i.e. using utility values for pre-progression and post-progression from the talquetamab base case approach), as shown in Table 71.

As shown in Table 72, the results of the severity modifier calculations demonstrate that talquetamab is not eligible for a severity modifier when compared to teclistamab, based on absolute and proportional QALY shortfalls of [redacted] years and [redacted], respectively, which are less than the thresholds of 12 and 0.85. While these values do not meet the severity modifier threshold, they still underline the severity and current unmet needs TCE RRMM. Even with teclistamab treatment, TCE RRMM patients would still qualify for the previous NICE end-of-life criteria (which required a median OS of less than 24 months).[193]

Table 71: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Starting age (mean)	[redacted]	Section 3.2.1
Proportion of female patients (%)	41.6	Section 3.2.1
Health state utility: pre-progression, mean (SE)	[redacted]	Section 3.4.5
Health state utility: post-progression, mean (SE)	[redacted]	Section 3.4.5

Abbreviations: QALY: quality-adjusted life year; SE: standard error.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[46] Chari *et al.* 2025.[117]

Table 72: Summary of QALY shortfall analysis

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	[redacted]	[redacted]	1.0

Abbreviations: QALY: quality-adjusted life year.

3.7 Uncertainty

Despite a robust and thorough trial-vs-trial ITC approach, the use of single-arm trials may introduce bias into the results

As both MonumenTAL-1 and MajesTEC-1 are single-arm trials, an ITC was required to compare the efficacy of talquetamab and teclistamab. The results of this ITC informed the efficacy data that was incorporated in the economic model. As they rely on the assumption that all prognostic factors and treatment effect variables can be adjusted for, ITCs based on single-arm trials are inherently associated with some degree of uncertainty.

However, in this case, due to the similarities in trial design between MonumenTAL-1 and MajesTEC-1 and the availability of IPD for the trials, the IPD of patients in MajesTEC-1 could be adjusted for all 17 key covariates identified as relevant by consultant haematologists, and

therefore any uncertainty is anticipated to be minimal. Moreover, as discussed in Section 2.10.3, prior to adjustment to the 17 prognostic variables, there was very high overlap in the distribution of the MonumenTAL-1 and MajesTEC-1 patient populations (see Table 25) and the two cohorts were further aligned following adjustment. Following ATT-adjustment, all 17 key covariates had an SMD <0.2, clearly demonstrating that the MonumenTAL-1 and MajesTEC-1 patient populations were well balanced.

Long-term uncertainty with MonumenTAL-1 Cohort C survival data

With a median follow-up of 31.2 months for Cohort C, as of the most recent September 2024 DCO ([redacted]), long-term extrapolation of OS, PFS and TTD data from the MonumenTAL-1 trial were required for the economic analyses, which is inevitably associated with uncertainty.[46, 119] However, the approach to modelling talquetamab long-term survival is anchored on the teclistamab curves, which were recently reviewed and accepted as part of TA1015.[194] Talquetamab long-term survival estimates were derived from the teclistamab curves using empirical data from robust trial-vs-trial ITCs of talquetamab versus teclistamab, which represent the highest grade of indirect evidence available assessing the relative effects between talquetamab and teclistamab. This approach therefore reduces any uncertainty associated with the long-term survival extrapolations for talquetamab.

Additionally, scenario analyses demonstrated that alternative plausible approaches to modelling talquetamab long-term survival (i.e. through the use of individually fitted curves) suggested that the base case economic analysis results may in fact be conservative (as detailed in Section 3.11.3).

3.8 Managed access proposal

This submission does not have a proposal for managed access – the data for talquetamab in this submission are based on the [redacted] of the MonumenTAL-1 trial (September 2024 DCO).

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 73.

Table 73: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs and benefits)	3.5%	Section 3.2.2
Time horizon	Lifetime (40 years)	
Patient baseline characteristics		
Mean age, years	[redacted]	

Proportion of female patients (%)	41.6				Section 3.2.1
Mean body weight, kg	[redacted]				
Mean BSA, m^2	[redacted]				
Survival inputs					
	PFS	**OS**	**TTD**	**QW/Q2W Dose Switching**	Section 3.3.2−3.3.5
Talquetamab	[redacted] PFS HR applied to teclistamab PFS curve	[redacted] OS HR applied to teclistamab OS curve	[redacted] TTD HR applied to teclistamab TTD curve	N/A	
Teclistamab	Calibrated LogNormal	Calibrated LogNormal adjusted to UK clinical practice (two-stage adjusted)	Calibrated LogNormal	Gompertz	
AEs					
	Talquetamab	**Teclistamab**			Section 3.3.1
Anaemia	25.3%	[redacted]			
Hypertension	[redacted]	[redacted]			
Hypokalaemia	[redacted]	[redacted]			
Hypophosphatemia	[redacted]	[redacted]			
Infection	[redacted]	[redacted]			
Leukopenia	[redacted]	[redacted]			
Lymphopenia	[redacted]	[redacted]			
Neurotoxicity	[redacted]	[redacted]			
Neutropenia	21.4%	[redacted]			
Pneumonia	[redacted]	[redacted]			
Rash	5.2%	[redacted]			
Thrombocytopenia	18.2%	[redacted]			
Weight loss	5.8%	[redacted]			
Utility inputs					
PFS (SE)	[redacted]				Section 3.4.5
PPS (SE)	[redacted]				
Adverse event disutility					
	Utility decrement	**Duration of AE (days)**			Section 3.4.4
Anemia	-0.3100	[redacted]			
Hypertension	0.0000	[redacted]			
Hypokalemia	-0.2000	[redacted]			
Hypophosphatemia	-0.1500	[redacted]			

Infection	-0.1900	[redacted]	
Leukopenia	-0.0700	[redacted]	
Lymphopenia	-0.0700	[redacted]	
Neurotoxicity	[redacted]	[redacted]	
Neutropenia	-0.1500	[redacted]	
Pneumonia	-0.1900	[redacted]	
Rash	-0.0325	[redacted]	
Thrombocytopenia	-0.3100	[redacted]	
Weight loss	0.0000	[redacted]	
Resource Use			
	PFS (on Tx)	**PFS (off Tx)**	**PD**
Haematologist visit	0.23	0.08	0.08
Full blood count	0.21	0.21	0.39
Biochemistry	0.19	0.19	0.33
Drug acquisition costs			
Talquetamab 3 mg/1.5 mL solution for injection	List price: £326.41 PAS price: [redacted]		
Talquetamab 40 mg/1 mL solution for injection	List price: £4,352.00 PAS price: [redacted]		
Teclistamab 30 mg/3 mL solution for injection	List price: £775.14 PAS price: [redacted]		
Teclistamab 153 mg/1.7 mL solution for injection	List price: £3,952.78 PAS price: [redacted]		
Co-medication costs			
Co-medication	**Cost per admin**		
Paracetamol (acetaminophen)	£0.02		
Diphenhydramine	£0.39		
Dexamethasone PO	£0.49		
Co-medication usage	**Talquetamab**	**Teclistamab**	
Paracetamol (acetaminophen)	100%	100%	
Diphenhydramine	100%	100%	
Dexamethasone PO	100%	100%	
IVIg usage	**Mean number of doses**	**Proportion of patients**	
Talquetamab	9.00	[redacted]	
Teclistamab	9.00	[redacted]	
IVIg costs	**Unit cost**		
IVIg (Octagram)	£690.00		
Administration costs (per admin)			

Section 3.5.2	
Section 3.5.1	
Section 3.5.1	
Section 3.5.1	

Complex first IV infusion	£554.23		Section 3.5.2
Other IV administration	£250.77		
Each SC administration	£108.90		
Oral drug initiation	£247.13		
Oral drug subsequent	£0.00		
Monitoring costs			
Haematologist visit	£204.32		Section 3.5.2
Full blood count	£6.95		
Biochemistry	£7.31		
End of life costs	£13,314.00		
AE costs			
Anaemia	£1,772.73		Section 3.5.3
Hypertension	£774.04		
Hypokalaemia	£2,061.89		
Hypophosphatemia	£2,061.89		
Infection	£2,528.21		
Leukopenia	£2,058.10		
Lymphopenia	£2,058.10		
Neurotoxicity	£7,310.00		
Neutropenia	£2,522.56		
Pneumonia	£1,367.85		
Rash	£511.89		
Thrombocytopenia	£2,515.70		
Weight loss	£577.91		
Subsequent treatment distribution			
Treatment	**Talquetamab**	**Teclistamab**	
Cyclophosphamide + Dexamethasone	[redacted]	[redacted]	Section 3.5.4
Dexamethasone	[redacted]	[redacted]	
Bendamustine	[redacted]	[redacted]	
Cisplatin + Etoposide + Cyclophosphamide + Dexamethasone	[redacted]	[redacted]	
Melphalan	[redacted]	[redacted]	
Melphalan + Dexamethasone	[redacted]	[redacted]	
Cyclophosphamide + Pomalidomide + Dexamethasone	[redacted]	[redacted]	
Pomalidomide + Dexamethasone	[redacted]	[redacted]	

Bortezomib + Cyclophosphamide + Dexamethasone	[redacted]	[redacted]	
Doxorubicin + Vincristine + Dexamethasone	[redacted]	[redacted]	
Lenalidomide + Dexamethasone	[redacted]	[redacted]	
Selinexor + Dexamethasone	[redacted]	[redacted]	
Methylprednisolone	[redacted]	[redacted]	
Teclistamab	[redacted]	[redacted]	
Subsequent treatment duration (months)			
Treatment	**Talquetamab**	**Teclistamab**	
Cyclophosphamide + Dexamethasone	4	4	Section 3.5.4
Dexamethasone	4	4	
Bendamustine	4	4	
Cisplatin + Etoposide + Cyclophosphamide + Dexamethasone	4	4	
Melphalan	4	4	
Melphalan + Dexamethasone	4	4	
Cyclophosphamide + Pomalidomide + Dexamethasone	4	4	
Pomalidomide + Dexamethasone	4	4	
Bortezomib + Cyclophosphamide + Dexamethasone	4	4	
Doxorubicin + Vincristine + Dexamethasone	4	4	
Lenalidomide + Dexamethasone	4	4	
Selinexor + Dexamethasone	4	4	
Methylprednisolone	4	4	
Teclistamab	[redacted]	-	

Abbreviations: AE: adverse event; BSA: body surface area; HR: hazard ratio; IV: intravenous; IVIg: intravenous immunoglobulin; N/A: not applicable; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; PO: per os; QW/Q2W: once weekly/bi-weekly; SC: subcutaneous; SD: standard deviation; SE: standard error; TTD: time to treatment discontinuation; Tx: treatment.

3.9.2 Assumptions

A summary of the assumptions utilised in the base case economic analysis can be found in Table 74.

Table 74: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Survival models		
OS, PFS and TTD curves	Teclistamab OS, PFS and TTD is modelled by independent extrapolation of the OS data from MajesTEC-1, using the calibrated LogNormal curve, as accepted by the Committee in TA1015.[194] Talquetamab OS, PFS and TTD is modelled by applying the OS HR estimated from ITC for talquetamab versus teclistamab (post-two stage adjustment for OS) to the teclistamab extrapolation described above.	The modelling of teclistamab OS, PFS and TTD was aligned with and builds upon the Committee accepted approach in TA1015.[194] The trial versus trial ITC results represent the highest grade of evidence estimates of the relative effects between talquetamab and teclistamab, and therefore it was considered most appropriate to apply the HR from the ITCs (two-stage adjusted for OS) to the extrapolations for teclistamab OS. The Schoenfeld residual plot was horizontal with a p-value >0.05 for OS, PFS and TTD, providing no evidence that the PH assumption should be rejected, in turn justifying the HR approach.
Two-stage OS subsequent treatment adjustment	Owing to the international nature of MajesTEC-1 and MonumenTAL-1, patients received subsequent therapies which are not available in routine UK clinical practice. The effects of these subsequent treatments on OS were removed using the two-stage OS adjustment approach outlined in NICE TSD16 to inform the economic base case.[178]	This two-stage OS adjustment is in line with the accepted approach in TA1015, wherein the teclistamab OS data was similarly adjusted for patients initiating a subsequent treatment not available in routine UK clinical practice.[194] Following the two-stage OS adjustment, as detailed in Section 2.10.6, a range of scenario analyses exploring alternative subsequent treatment adjustments, demonstrated consistent OS HRs and ICERs in favour of talquetamab. The scenario analyses explored included (a) an 'All-Out' scenario, with the removal of non-UK subsequent therapies, including removal of subsequent teclistamab and talquetamab in MonumenTAL-1 and MajesTEC-1, respectively as well as (b) an 'All-In' scenario, which allowed for subsequent talquetamab in MajesTEC-1 to be considered. Results of these scenario analyses are presented above in Section 2.10.6 (OS ITC analyses) and Section 3.11.3 (cost-effectiveness results).
Costs		

Hospitalisation for talquetamab and teclistamab step-up dosing	A hospitalisation period of 8 days and 6 days were assumed for the step-up dosing regimen of talquetamab and teclistamab respectively.[1]	The hospitalisation periods for teclistamab and talquetamab are aligned with the respective SmPCs and the approach taken in TA1015 for teclistamab.[1, 194, 211]
Teclistamab dose switching	A reduced dose frequency of teclistamab (i.e. biweekly dosing) was modelled starting from 52 weeks, using the Gompertz dose switching curve, as accepted in TA1015. The remaining patients were assumed to remain on a weekly dosing regimen	As per the Committee's preferred approach in TA1015, a reduced dose frequency of teclistamab (i.e. biweekly dosing) was modelled from 52 weeks using the MajesTEC-1 data (IPTW ATT-weighted) to model the reduced dose frequency at different time points from 52 weeks onwards.[194]
Dose skipping	The model included a proportion of talquetamab doses being skipped based on MonumenTAL-1, wherein [redacted]% of talquetamab doses were skipped.[46] A proportion of teclistamab doses being skipped was also modelled based on MajesTEC-1, wherein [redacted]% of teclistamab doses were skipped in line with the Committee preferred assumptions for TA1015.[40]	In line with the Committee accepted approach in TA1015, skipped doses of both teclistamab and talquetamab were accounted for in the base case.[194]
Proportion of patients receiving subsequent treatment and distribution of subsequent treatments	The proportion of patients receiving subsequent treatments following progression on teclistamab and talquetamab is based on MajesTEC-1 and MonumenTAL-1, respectively.[40, 46] The distribution of subsequent treatments was based on the trials but adjusted following the removal of non-routine UK therapies.	MonumenTAL-1 and MajesTEC-1 represent the best evidence sources to inform the proportion of patients receiving subsequent treatment following progression on talquetamab and teclistamab, respectively. However, it is acknowledged that patients in MonumenTAL-1 and MajesTEC-1 received therapies which are not available in routine UK clinical practice and therefore, the costs for subsequent treatment have been calculated based on the subsequent treatment distribution following the removal of non-routine UK therapies in line with the approach taken in TA1015.[194]

Subsequent treatment duration	Following disease progression on talquetamab or teclistamab, patients were assumed to receive subsequent treatments (other than teclistamab) for a mean duration of 4 months, in line with Yong *et al.* 2016 and TA1015.[194, 230], The mean duration of treatment on teclistamab was assumed to be [redacted] (SE: [redacted]) months, based on MonumenTAL-1.[46]	The subsequent treatment duration assumption of 4 months for the non-teclistamab subsequent therapies is in line with the Committee accepted approach in TA1015.[194] It is acknowledged that given that teclistamab has been shown to be more effective than the other subsequent treatment options, patients receiving teclistamab are likely to receive treatment for a longer duration and therefore, it was deemed more appropriate to model the duration of treatment on teclistamab based on MonumenTAL-1 trial data.[46] Likewise, in the 'All-In' scenario analysis, the duration of subsequent treatment with talquetamab after teclistamab was modelled based on MonumenTAL-1 trial data ([redacted] [SE: [redacted]]) months).[46]
IVIg	Ig costs were modelled in line with the usage of IV Ig observed in MajesTEC-1 ([redacted]%) and MonumenTAL-1 (Cohort C; [redacted]%)].[40] The average number of doses was assumed to be 9 doses, in line with the Committee accepted approach in TA1015.[194]	In the absence of available data on Ig usage in TCE RRMM patients in UK clinical practice, the MajesTEC-1 and MonumenTAL-1 trials, in addition to the duration of IVIg use agreed in TA1015 were considered as the best source of data to inform Ig usage in the economic model.[40]
Utility values		
Treatment-independent HSUVs	In the base case analysis, treatment-independent HSUVs, derived from MonumenTAL-1 were used to inform the utility values for teclistamab and talquetamab.	Given that talquetamab and teclistamab are both BsAbs and dexamethasone-free regimens, it was deemed appropriate to assume equal utilities. Utility values for the PF and PP health states were derived using EQ-5D-5L data in MonumenTAL-1.[46] The use of treatment-independent HSUVs informed by MajesTEC-1 was explored in a scenario analysis (see Section 3.11.3).[45]
AE disutilities	In the base case analysis, to account for the impact of treatment-specific of AEs, a one-off decrement in utilities was applied based on the proportion and duration of AEs experienced by patients in MonumenTAL-1 and MajesTEC-1.[40, 46] Utility decrements were informed by published literature, in line with the Committee accepted approach in TA1015.[194]	Whilst both talquetamab and teclistamab are BsAbs and dexamethasone-free monotherapies, differences in the safety profile of both therapies remain. To account for the differences in AEs experienced by patients receiving each treatment, it was deemed appropriate to apply a one-off decrement in utilities.

Abbreviations: AEs: adverse events; BsAbs: bispecific antibodies; CRS: cytokine release syndrome; EQ-5D-5L: EuroQol five dimensions five levels; HR: hazard ratio; HSUVs: health state utility values; IVIg: intravenous immunoglobulin; NICE: National Institute for Health and Care Excellence; OS: overall survival; PF: progression-free; PFS: progression-free survival; PP: post-progression SmPC: Summary of Product Characteristics; TTD: time to treatment discontinuation; TSD: Technical Support Document.

3.10 Base-case results

Results of the economic analysis are presented in Section 3.10.1 below.

3.10.1 Base-case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness results for talquetamab versus teclistamab, both at list price and with-PAS price, are presented in Table 75 and Table 77, respectively. The probabilistic base case cost-effectiveness results, both at list price and with-PAS price, are presented in Table 76 and Table 78, respectively.

The with-PAS deterministic base case cost-effectiveness results show that over a 40 year time horizon, the total costs associated with talquetamab are estimated to be [redacted], compared with [redacted] for patients treatment with teclistamab (incremental cost of [redacted]). The total QALYs are estimated to be higher for patients receiving talquetamab than for patients receiving teclistamab ([redacted] versus [redacted]; incremental QALYs: [redacted]), resulting in an ICER for talquetamab of £29,277 per QALY gained versus teclistamab. The with-PAS deterministic base case cost-effectiveness results are consistent with the probabilistic results.

In the probabilistic base case analysis, talquetamab (with PAS) was associated with [redacted] more QALYs and increased total costs of [redacted] in comparison to teclistamab (with PAS), resulting in an ICER for talquetamab of £30,386 per QALY gained versus teclistamab. Taken together, the deterministic and probabilistic with-PAS results demonstrate that talquetamab represents a cost-effective use of NHS resources in the UK.

Notably, in both the deterministic and probabilistic with-PAS base case analyses, the positive incremental LYs (3.22 and 3.29 for the deterministic and probabilistic analyses, respectively) and QALYs ([redacted] and [redacted] for both the deterministic and probabilistic analyses, respectively) associated with talquetamab versus teclistamab highlight the improvements in both quality and length of life that talquetamab may offer to patients in this setting who are ultimately nearing the end of their terminal illness.

Table 75: Deterministic base-case results (talquetamab and teclistamab list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.27	[redacted]					
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£64,459	-2.25

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 76: Probabilistic base-case results (talquetamab and teclistamab list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.34	[redacted]					
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£64,760	-2.32

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 77: Deterministic base-case results (talquetamab and teclistamab PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.27	[redacted]					
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£29,277	0.05

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 78: Probabilistic base-case results (talquetamab and teclistamab PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.34	[redacted]					
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£29,246	0.05

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

3.11 Exploring uncertainty

Parameter uncertainty in the model was assessed via probabilistic and deterministic sensitivity analyses, the results of which are presented in Section 3.11.1 and Section 3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.11.3. Of note, this section focusses on with-PAS comparisons of talquetamab versus teclistamab to model uncertainty, as the with-PAS analyses are more informative for decision-making.

Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

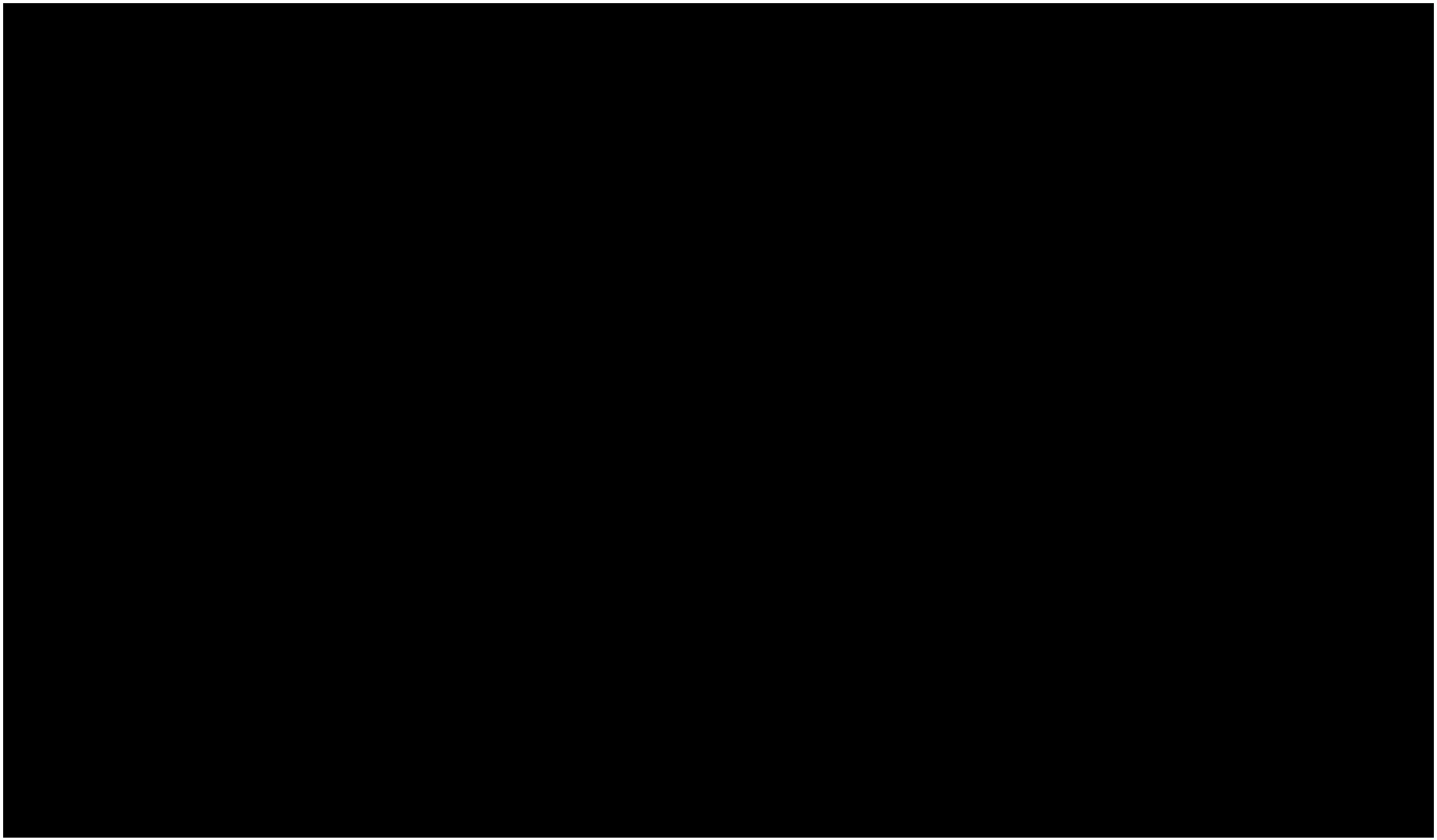
3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions. Estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, the model assumes 10% of the mean value represents the SE.

INHB convergence plots are provided for the with-PAS price of talquetamab and teclistamab in Figure 36 below. The plots demonstrate that the cumulative INHB converges after approximately 400 iterations for the with-PAS analysis.

The probabilistic cost-effectiveness planes for talquetamab (with-PAS) versus teclistamab (with-PAS) is presented in Figure 37. The cost-effectiveness acceptability plots are presented in Figure 38; the PSA found the probability of talquetamab being a cost-effective use of NHS resources to be [redacted] and [redacted] at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 36: INHB convergence plot (talquetamab and teclistamab PAS price)



Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme.

Figure 37: Probabilistic cost-effectiveness plane for talquetamab versus teclistamab (talquetamab and teclistamab PAS price)

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

Figure 38: Cost-effectiveness acceptability curve for talquetamab versus teclistamab (talquetamab and teclistamab PAS price)

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, a DSA was conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. For certain parameters where SEs of the mean were available, the lower and upper limits were defined by the 95% CI around the mean. In the absence of 95% CI, the inputs were arbitrarily varied by ±10%.

A tornado diagram showing the top 10 most influential parameters on the incremental net health benefit (INHB) for talquetamab (with-PAS) versus teclistamab (with-PAS) is presented in Figure 39. The incremental NHB was found to be most sensitive to the HRs applied to derive the talquetamab TTD and OS curves from the teclistamab TTD and OS curves and the PPS utility values; these top three most influential parameters are discussed sequentially below. The DSA demonstrates minimal uncertainty around all other parameters evaluated.

HR approach – talquetamab versus teclistamab OS and TTD

Uncertainty around long-term estimates of OS and TTD (in addition to PFS) is an inherent limitation of the evidence base for all oncology appraisals. However, the HR approach taken leverages results from a robust trial-versus-trial ITC conducted between talquetamab and teclistamab, and therefore reflects the highest grade of indirect evidence available on the relative effects of the two treatments. The ITCs derived for each endpoint were highly consistent across an extensive range of alternative ITC scenario analyses, supporting the robustness of the ITC results. The HR approach also leveraged long-term survival estimates of teclistamab that have been reviewed and agreed upon by the NICE committee as part of TA1015;[194] the combination of these factors reduces uncertainty associated with the long-term survival extrapolations for talquetamab.

As shown in Figure 39, the uncertainty surrounding the HR approach for talquetamab versus teclistamab OS and TTD is observed in both directions. It is also important to note that as OS and TTD (in addition to PFS) are inherently interlinked parameters (see Section 3.3.5), with changes in one parameter likely also leading to changes in another, the uncertainty around the HRs cannot be fully measured by considering the one-way sensitivity analysis. As such, the PSA presented above may provide a more meaningful assessment of the uncertainty surrounding these variables given the PSA represents situations in which all parameters are varied in combination. As discussed above, the results of the PSA demonstrate that the deterministic and probabilistic base case ICERs are highly consistent, highlighting that the estimated cost-effectiveness of talquetamab versus teclistamab is stable, and not significantly influenced by uncertainty surrounding the parameters. Additionally, as demonstrated by the scenario analyses (Section 3.11.3), scenarios exploring three independently fitted curves to talquetamab OS, PFS and TTD data resulted in improved (i.e. reduced) ICERs as compared with the base case analysis. As such, the HR approach in the base case likely results in a conservative estimate of the true cost-effectiveness of talquetamab in UK clinical practice.

PPS utility

PPS utility values were derived using EQ-5D-5L data in MonumenTAL-1, based on the crosswalk method reported by Hernández Alava et al. (2017) to map EQ-5D-5L dimension scores from the MonumenTAL-1 trial to utilities using the UK EQ-5D-3L value set. As such, the utility values informing the economic analyses represent the most robust and relevant utility data available for

the modelled population. Of note, a scenario to explore the uncertainty around the choice of PPS utility was conducted (see Section 3.11.3, Scenario 3), whereby PPS HSUVs for teclistamab and talquetamab were derived from the EQ-5D data from MajesTEC-1 (accepted as part of TA1015); this scenario analysis demonstrates that use of an alternative plausible PPS utility has a minimal impact on the economic results (Section 3.11.3).

Figure 39: DSA tornado diagram for talquetamab versus teclistamab, INHB (talquetamab and teclistamab PAS price)

Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme; PFS: progression-free survival; PPS: post-progression survival SC: subcutaneous.

3.11.3 Scenario analysis

As described in Section 3.11, scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. A complete list of the scenario analyses explored along with the rationale for their selection is provided Table 79.

Table 79: Summary of scenario analyses

Model element	Base case	Scenario analysis	Justification
Time horizon	40 years	1a: 25 years	This scenario analysis explored an alternative time horizon duration, in line with other NICE appraisals in MM (elranatamab [TA1023] and BelMaf [ID2701])[8, 231]
		1b: 30 years	This scenario analysis explored an alternative time horizon duration of 30 years, in line with the NICE appraisal for SelDex [TA970].[6]
Talquetamab efficacy data source	Informed by Cohort C of MonumenTAL-1 wherein patients received talquetamab following a Q2W dosing regimen	2: Weighted split of 90%/10% between Cohort C and Cohort A of MonumenTAL-1 wherein patients in Cohort A and C received talquetamab on QW and Q2W dosing regimens respectively	Talquetamab is licensed for both QW and Q2W dosing regimens.[1] Whilst the Q2W dosing regimen is considered to be most reflective of the anticipated dosing regimen in the UK given the reduced resource impact and lower incidence of AEs, a scenario analysis was explored to account for the plausibility of patients receiving talquetamab on a QW dosing regimen. Clinical feedback indicated that 90% of patients would receive Q2W dosing regimens and 10% would receive QW dosing regimen. As per the base case approach, long-term survival estimates for talquetamab were derived by applying HRs to the calibrated survival extrapolations for teclistamab (see Section 3.3 for detailed methodology). The OS, PFS and TTD HRs applied in this scenario analysis are presented in the table below.

	Talquetamab	Teclistamab (as per TA1015)[194]

Model element	Base case	Scenario analysis	Justification
			OS: Derived by applying the two stage-adjusted ITC OS HR ([redacted] [95% CI: [redacted]) to the teclistamab OS curve — Calibrated LogNormal[a] PFS: Derived by applying the ITC PFS HR ([redacted] [95% CI: [redacted]) to the teclistamab PFS curve — Calibrated LogNormal[b] TTD: Derived by applying the ITC TTD HR ([redacted] [95% CI: [redacted]) to the teclistamab TTD curve — Calibrated LogNormal[c]
Utility values	HSUVs were assumed to be equal for both teclistamab and talquetamab, and derived from EQ-5D data from MonumenTAL-1: Pre-progression, mean (SE): [redacted] ([redacted]) Post-progression, mean (SE): [redacted] ([redacted])	3: HSUVs for teclistamab and talquetamab were derived from the EQ-5D data from MajesTEC-1: Pre-progression, mean (SE): [redacted] ([redacted]) Post-progression, mean (SE): [redacted] ([redacted])	This scenario analysis explores an alternative source of utility data (i.e. MajesTEC-1) to inform the HSUVs for both teclistamab and talquetamab.
AE disutilities	One-off decrement applied based on duration of AEs for talquetamab and teclistamab informed by MonumenTAL-1	4: No AE disutilities applied	In the base case analysis, a one-off decrement was applied to account for the impact of treatment-specific AEs, especially given that equal HSUVs have been assumed for teclistamab and talquetamab. A scenario analysis in which no AE disutilities are applied was therefore conducted to explore the impact of this assumption.
Subsequent treatment	Proportion of patients receiving subsequent therapies based on MonumenTAL-1 and MajesTEC-1, with the distribution of subsequent treatment informed by routine subsequent treatments	5: Reweighting all non-teclistamab subsequent treatments to have a distribution split of 70%/20%/10% for PomDex/PanBorDex/SelDex	Clinical expert feedback received in TA1015 indicated that PomDex, PanBorDex and SelDex were the main alternative treatment options used in UK clinical practice.[194] They estimated that the treatment distribution split for PomDex/PanBorDex/SelDex to be 70%/20%/10%.[194] Therefore, a scenario analysis was further explored wherein the non-teclistamab subsequent treatments were reweighted to best reflect this clinical expert feedback. Given the

Model element	Base case	Scenario analysis	Justification
	available in the UK received by patients in both trials. Patients who progressed on teclistamab would therefore, not receive talquetamab whilst patients who progressed on talquetamab could receive teclistamab since this is reflective of current UK clinical practice, in which talquetamab is not yet reimbursed.		similarity in efficacy of non-BsAb subsequent treatments, only costs were adjusted for in this scenario. A summary of the costs associated with each of the subsequent treatments is provided in Appendix I.
		6a: 'All-Out' scenario; Removal of all non-routine UK specific treatment, as well as removing teclistamab from MonunenTAL-1	Whilst the base case is reflective of the current UK clinical practice, teclistamab has demonstrated better survival outcomes compared to other subsequent treatment options, as per TA1015.[194] The base case takes on an NHS England perspective and current UK clinical practice whereby patients who have progressed on talquetamab would have access to teclistamab whereas patients who have progressed on teclistamab would not have access to a BsAb like talquetamab or be re-treated with teclistamab. Therefore, to account for the OS impact of availability of teclistamab as a subsequent BsAb treatment option for patients who have progressed on talquetamab, a scenario analysis was explored whereby patients were unable to receive teclistamab following progression on talquetamab. The subsequent treatment distributions are in line with Table 70, except with teclistamab removed as a subsequent treatment option from MonumenTAL-1 and all other treatments reweighted accordingly. A summary of the costs associated with each of the subsequent treatments is provided in Appendix I. As per the base case approach, long-term survival estimates for talquetamab were derived by applying HRs to the calibrated survival extrapolations for teclistamab (see Section 3.3 for detailed methodology). The OS HR applied in this scenario analysis was [redacted] (95 CI: [redacted])

Model element	Base case	Scenario analysis	Justification
		6b: 'All-In' scenario: Removal of all non-routine UK specific treatment, but allowing subsequent talquetamab following teclistamab, vice versa	An exploratory scenario analysis was included to illustrate the impact of patients receiving subsequent talquetamab following teclistamab treatment to reflect anticipated future UK clinical practice once talquetamab is reimbursed. The subsequent treatment distributions are in line with Table 70, except with [redacted]% of patients receiving talquetamab following treatment with teclistamab, and with all other treatments reweighted accordingly. A summary of the costs associated with each of the subsequent treatments is provided in Appendix I. As per the base case approach, long-term survival estimates for talquetamab were derived by applying HRs to the calibrated survival extrapolations for teclistamab (see Section 3.3 for detailed methodology). The OS HR applied in this scenario analysis was [redacted] (95% CI: [redacted]).
Talquetamab PFS/OS/TTD extrapolation	Talquetamab PFS/OS/TTD extrapolations derived by applying HRs from the ITCs of talquetamab vs teclistamab, extrapolations for teclistamab from TA1015.[194] For OS specifically, in the base case analysis, talquetamab was modelled by applying the two-stage adjusted OS ITC HR to the teclistamab extrapolation, to account for subsequent	7a: Talquetamab PFS/OS/TTD: Individually fitted LogNormal	Whilst the base case analysis approach is considered the most appropriate approach to modelling long-term survival estimates for talquetamab, scenario analyses explored individually fitted curves modelled for talquetamab PFS, OS and TTD. As noted in Section 3.3, it is important to select the same extrapolation curves (and thus curves with the same underlying hazard function) across the three outcomes given OS, PFS and TTD are three inherently interlinked outcomes. Firstly the LogNormal curve was selected based on statistical fit based on BIC/AIC; for talquetamab PFS and TTD, the LogNormal provided the best statistical fit, and provided the second best statistical fit (after

Model element	Base case	Scenario analysis	Justification
	treatments that are not routinely available in the UK.		the Gompertz) for OS (see Appendix K). Of note, the difference in AIC/BIC between the LogNormal and Gompertz curves for the talquetamab OS extrapolations is too small (<1) to conclude that there are any material differences between the two curves and how well they fit the data. Thus, the LogNormal was selected for all three endpoints. Selection of the LogNormal curve for talquetamab aligns to the approach used to model teclistamab in the base case analysis (i.e. using the LogNormal, which was based on reviewed and accepted approaches in TA1015).[194] This approach also aligns to guidance in NICE TSD 14,[164] which emphasises that substantial justification would be required to fit different types of parametric models to different treatment arms. For two alternative scenarios, the Weibull and Gamma curves were individually fitted to talquetamab PFS, OS and TTD. The Weibull and Gamma curves were selected in order to further explore the impact of choosing alternative curves to predict long-term outcomes as they provide lower estimates of talquetamab OS, and therefore reflect more conservative estimates of talquetamab long-term survival. Of note however, given the talquetamab and teclistamab are both BsAbs, it is unclear whether there is sufficient justification to be using different types of extrapolation for the two treatments. No scenario analyses were conducted using the exponential distribution, given the exponential provides the worst statistical fit to the observed data, has an extremely poor visual fit, and assumes a constant hazard of death. Given the predominantly incurable nature of MM, the exponential distribution represents a clinically implausible curve and was
		7b: Talquetamab PFS/OS/TTD: Individually fitted Weibull	
		7c: Talquetamab PFS/OS/TTD: Individually fitted Gamma	

Model element	Base case	Scenario analysis	Justification
			therefore excluded from consideration for the scenario analyses.

Abbreviations: AE: adverse events; AIC: Akaike Information Criterion; Belmaf: belantamab mafodotin; BIC; Bayesian information criterion; BsAb: bi-specific antibody; CI: confidence interval; EQ-5D: EuroQoL-5 dimensions; HSUV: health-state utility value; NHS: National Health Service; OS: overall survival; PanBorDex: panobinostat with bortezomib and dexamethasone; PomDex: pomalidomide with dexamethasone; Q2W: every two weeks; QALY: quality-adjusted life year; QW: every week; SE:standard error; SelDex: selinexor with dexamethasone; TA: technology appraisal; TSD: Technical Support Document; UK: United Kingdom.

None of the scenario analyses changed the cost-effectiveness conclusions of the base case analysis; the with-PAS scenario analyses all resulted in ICERs of ~£30,000 per QALY gained or lower, and the changes in INHB were minor across most analyses, demonstrating that the base case results are generally associated with minimal uncertainty. The INHB was found to be most sensitive to the individually fitted curves for talquetamab PFS/OS/TTD, although notably the uncertainty was in favour of talquetamab for all three curve choices (Weibull, Gamma and LogNormal), with the INHB increasing substantially from the base case results for all three scenarios. Additionally, all scenario analyses demonstrated positive incremental QALYS (range: [redacted]) associated with talquetamab versus teclistamab, further emphasising the improvements in both quality of life that talquetamab may offer to patients nearing the end of their terminal illness.

Table 80: Summary of scenario analysis results (talquetamab and teclistamab PAS price) – probabilistic

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	**£29,246**	**0.05**
1a	Time horizon: 25 years	[redacted]	[redacted]	£29,436	0.04
1b	Time horizon: 30 years	[redacted]	[redacted]	£29,228	0.05
2	Talquetamab efficacy data source: Weighted split 90%/10% Cohort C and A	[redacted]	[redacted]	£29,511	0.03

3	Utility values: Derived from MajesTEC-1	[redacted]	[redacted]	£30,784	-0.05
4	AE disutilities: No decrements applied	[redacted]	[redacted]	£29,387	0.04
5	Subsequent treatment: Reweighting non-teclistamab subsequent treatment (i.e. 70%/20%/10% split for PomDex/PanBorDex/SelDex)	[redacted]	[redacted]	£30,891	-0.06
6a	Subsequent treatment: Removal of all non-routine UK treatment, as well as removing teclistamab from MonumenTAL-1 – All Out	[redacted]	[redacted]	£31,150	-0.07
6b	Subsequent treatment: Removal of all non-routine UK treatment, but allowing subsequent talquetamab following teclistamab, vice versa – All In	[redacted]	[redacted]	£29,055	0.06
7a	Talquetamab PFS/OS/TTD: Individually fitted Lognormal	[redacted]	[redacted]	£24,467	0.44
7b	Talquetamab PFS/OS/TTD: Individually fitted Weibull	[redacted]	[redacted]	£23,434	0.34
7c	Talquetamab PFS/OS/TTD: Individually fitted Gamma	[redacted]	[redacted]	£25,848	0.18

Abbreviations: AE: adverse events; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; OS: overall survival; PanBorDex: panobinostat with bortezomib and dexamethasone; PFS: progression-free survival; PomDex: pomalidomide with dexamethasone; QALY: quality-adjusted life year; SelDex: selinexor with dexamethasone; TTD: time to treatment discontinuation; UK: United Kingdom.

3.12 Subgroup analysis

For the reasons detailed in Section 1.1, no subgroups were considered in this appraisal, and therefore in the cost-effectiveness analysis.

3.13 Benefits not captured in the QALY calculation

Introduction of a novel mechanism of action of MM treatment

As outlined in Section 1.3.4, due to the disease pathophysiology of RRMM, patients do not typically receive treatments with the same drug target as a previous treatment until all other treatment classes are exhausted. This is because recycling of existing therapies in RRMM is likely to have limited efficacy, as patients are re-exposed to treatments or classes of agents that they have previously developed resistance to. The introduction of treatments with novel mechanisms of actions for patients with TCE RRMM is therefore of utmost importance to both patients and clinicians.[16]

The introduction of BCMA-targeting BsAbs represented a step-change in improving the treatment options for TCE RRMM patients and is expected to provide patients with an additional 12.4 months life on average, compared to the previous SoC in this setting (PomDex, PanBorDex and SelDex).[194] However, MM remains predominantly an incurable disease, and subsequently, the prognosis of TCE RRMM patients still remains poor (with a median OS of 22.2 months as per the MajesTEC-1 trial).[40] Consequently, even following the survival improvements associated with teclistamab, TCE RRMM patients would still qualify for the previous NICE end-of-life criteria (which required a median OS of less than 24 months).[193] As demonstrated in Section 2.10.5, talquetamab, with its' novel GPRC5D target has an OS benefit compared to teclistamab, and if reimbursed, will provide clinicians with the additional efficacious therapy they aspire for by prolonging the lives of patients.

Additionally, the RRMM treatment landscape is evolving, with ongoing changes in therapeutic approaches, including the potential introduction of more BCMA-targeted treatments earlier in the treatment pathway in the UK.[106, 107, 112-114] Clinicians have noted that there will therefore be an increasing unmet need for non-BCMA treatments such as talquetamab. The benefits of the introduction of the GPRC5D-targeting mechanism with talquetamab is likely to increase with future advancements in the RRMM treatment landscape.

Value of additional treatment choice

As well as representing an efficacious treatment alternative for TCE RRMM patients, talquetamab will provide additional hope to TCE RRMM patients by providing them with the treatment choice they currently desire. As detailed in Section 1.3.3, providing patients with choice and allowing clinicians to tailor treatment to patients' individual needs is a fundamental aspect of NHS care and service, and is extremely important in giving patients an increased sense of control over their disease.[30, 31] Clinician feedback also stressed that there is a dire lack of treatment choice when patients become TCE. Patient organisation views received from Myeloma UK during TA1015 similarly echoed the lack of a real alternative treatments to BCMA-targeted BsAbs like teclistamab wherein patients indicated that "teclistamab was [their] only option. [They were] offered palliative care a few times".[194] Patients' increased hope and reductions in anxiety resulting from the availability of talquetamab as an additional treatment choice are not captured in the QALY calculation.

Value of lower infection rate

As discussed in Section 2.11.4, BCMA-targeting BsAbs are associated with higher rates of all-Grade and ≥Grade 3 infections, relative to other MM therapies, owing to their off-target effects on patients' B-cells and plasma cells.[32-36, 38, 39] The increased risk of infections is severely detrimental to patients' QoL, with one patient consulted by Myeloma UK stating that "*the social isolation due to the increased risk of infection has had the biggest impact.".*[194]

As detailed in Section 2.11.4, with its distinct GPRC5D target, that allows for longer term maintenance of immune function compared to BCMA-targeting treatments, talquetamab has a substantially lower rate of severe infections, as well as reduced infection-related mortality compared to BCMA-targeting BsAbs.[46] Patients receiving talquetamab are likely to experience a reduced infection-related anxiety due to social isolation compared to those receiving BCMA-targeting BsAbs, that is not captured in the QALY calculation.

Reduction in caregiver burden

The increased risk of infections with BCMA-targeting BsAbs is a cause of concern for both patients and their loved ones, who as discussed in Section 1.3.3, often provide informal care to RRMM patients. A recent study sponsored by J&J IM surveying 120 carers of patients with MM found that in total, [redacted]% of the carers were the partner or spouse of the patient.[97] With the flexible dosing regimen and improved infection-related safety profile associated with talquetamab, patients will be required to visit hospital less frequently, which consequently means the impact on their caregivers will also reduce. These beneficial impacts of talquetamab for carers are not captured in the QALY calculations.

Outpatient benefits

An additional conservative assumption in the submission is that patients receiving talquetamab receive the step-up doses in the inpatients setting. However, clinical practice is moving towards more patients receiving the talquetamab step-up dose in the outpatient setting. Administering talquetamab in the outpatient setting would increase bed space in hospitals and reduce healthcare resource requirements. Outpatient administration also has additional benefits for patients, as they are spared from hospital admission and the associated physical and emotional implications of this. It also means that caregivers do not have to travel to and from hospitals as much, thereby reducing the impact that caring has on their daily lives.

Opportunity to continue derive benefits from future innovations

Patients face uncertainty about future medical advances, and when they may occur, making life extension a valuable option that allows patients to benefit from unpredictable future advancements in their treatments. As highlighted in Section 1.3.4, the RRMM treatment landscape is constantly evolving, and additional therapies with alternative mechanisms of action will likely be approved for use in the future. With its OS benefit over teclistamab, talquetamab could extend the lives of patients long enough for them to benefit from subsequent innovative future advances in RRMM treatments that become available.[232] The potential additional QALYs that arise from future innovations are excluded from the analysis in this submission.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Face validity

Model validations were performed in alignment with best practices.[233] The model structure, source data and statistical analysis design were reviewed by external experts, including health economic and UK clinical experts in MM.

Internal validity

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks), based on the published TECH-VER checklist,[234] were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

External validity

Clinical feedback was also used to validate key inputs and assumptions utilised in the model, including subsequent treatment choices and monitoring frequencies. Where possible, UK sources were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted.[3]

3.15 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness evidence

The MonumenTAL-1 trial demonstrated the efficacy and safety of talquetamab in the TCE RRMM patient population. Talquetamab was associated with a higher ORR than teclistamab (69.5% versus 63.0%, respectively), which represents the highest magnitude of clinical benefit that can be achieved in orphan disease such as TCE RRMM based on the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies.[45, 46, 150] Treatment with talquetamab was associated with deep responses; as demonstrated by the 40.3% of patients who achieved a ≥CR, which is similar to the 46.1% of patients achieving this level of response with teclistamab in MajesTEC-1.[119, 212] Achieving this level of response following three previous lines of therapy will provide patients with a renewed sense of hope.

Though the introduction of BCMA-targeting BsAbs represented a step-change in the treatment of TCE RRMM, patient prognosis still remains modest and effective alternatives are needed to

prolong patients' lives. In a trial-vs-trial ITC comparing talquetamab and teclistamab, a statistically significant and clinically meaningful improvement in OS was observed for patients treated with talquetamab versus teclistamab, following the adjustment to remove the effect of non-routine UK subsequent treatment, with a [redacted] reduction in the risk of death over time (OS HR: [redacted]; 95% CI, [redacted], [redacted]). This clearly demonstrates that talquetamab represents an efficacious alternative treatment that patients and clinicians can consider, that will result in further improvements in prognosis for TCE RRMM patients. Sensitivity analyses performed in Section 2.10.6 demonstrated that the [redacted]. The QALY shortfall analysis revealed an absolute QALY shortfall of [redacted] QALYs, and a proportional QALY shortfall of [redacted] QALYs, representing the proportion of remaining QALYs that patients with TCE RRMM lose over their remaining lifetime. This result underscores the severity TCE RRMM patients and illustrates an unmet need that exists for alternative efficacious treatment options for these patients.

The improved efficacy results were reflected in the base case economic analysis, where talquetamab was associated with 3.22 LYG and [redacted] QALYs gained versus teclistamab (with-PAS deterministic analysis).

As detailed further in Section 3.13, the economic results presented in this submission omit certain key benefits associated with talquetamab that cannot be captured in the QALY calculations, including the value of hope associated with providing an additional treatment option for TCE RRMM patients, the reduced anxiety around contracting infections, and the reduction in caregiver burden, which all mean that the base case results likely represent a conservative estimate of the true cost-effectiveness of talquetamab in UK clinical practice.

The economic evaluation utilised the best available clinical evidence for talquetamab, MonumenTAL-1. In both the base case probabilistic and deterministic with-PAS analyses, results demonstrated an ICER for talquetamab of <£30,000 per QALY gained, translating to talquetamab representing a cost-effective treatment option compared to teclistamab. Additionally, the positive incremental QALYs ([redacted] and [redacted] for the deterministic and probabilistic analyses) and positive LYGs for teclistamab (3.22 and 3.29 for deterministic and probabilistic analyses, respectively) indicate that talquetamab provides additional clinically meaningful health benefits in terms of both quality and length of life to TCE RRMM patients in a cost-effective manner over teclistamab.

The PSA found the probability of talquetamab being cost-effective to be [redacted] and [redacted] at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The with-PAS DSAs highlight that the incremental NHB was most sensitive to the TTD and OS HR approach (talquetamab versus teclistamab) and the PPS utility value. However, overall, the base case results were found to be robust to uncertainty across all model parameters, as demonstrated by the close alignment of deterministic and probabilistic analyses. Scenario analyses conducted to address sources of uncertainty in the model additionally demonstrated that variations in the INHB were minimal across most analyses, including scenario analyses of alternative subsequent treatment distributions in which the effect of patients receiving subsequent treatments not relevant to UK clinical practice is removed (All-In/All-Out scenarios), which provides evidence that this does not represent a source of uncertainty in the cost-effectiveness analyses. Crucially, none of the scenario analyses resulted in meaningful changes to the cost-effectiveness conclusions of the base case analysis, with ICERs for talquetamab of ~£30,000 or less per QALY gained across all with-PAS scenario; talquetamab remained cost-effective versus teclistamab across all scenarios.

In fact, among the scenario analyses modelling individually fitted curves to talquetamab PFS, OS and TTD, the ICER for talquetamab versus teclistamab was reduced compared with the base case ICER, demonstrating that the base case cost-effectiveness analysis may be conservative.

Strengths

The cost-effectiveness analysis is associated with several strengths, the first being that many therapies for RRMM have been appraised by NICE.[194, 198, 201, 203] During model design and development, a review of relevant NICE evaluations was conducted, making it possible to take into account a number of learnings from previously developed models for RRMM, in addition to prior EAG and Committee preferences for methodological approaches in this area (e.g. TA889 and in particular TA1015), such as cost and resource use and the selection of HSUVs.[194, 235] In particular, the cost-effectiveness model for talquetamab is, where possible, aligned to the cost-effectiveness model (and associated Committee preferred assumptions) that was accepted by NICE during the development of TA1015.[194]

Additionally, the model was aligned to UK clinical practice where possible. For example, as detailed in Section 2.10.4, a two-stage OS adjustment was performed to remove the effect of patients receiving subsequent treatments not relevant to UK clinical practice, as well as removing subsequent talquetamab following teclistamab treatment in the base case analysis. As such, the costs of subsequent treatments are closely aligned to what could be expected in UK clinical practice, where talquetamab is not yet reimbursed. Consequently, the base case ICER is highly relevant to decision making.

Furthermore, the model closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully capture and discounting costs and benefits at a rate of 3.5% per annum.[236]

Limitations

A key limitation of the evidence base was the lack of direct data comparing talquetamab and teclistamab. To address this limitation, an ITC was conducted to obtain a relative efficacy estimate for talquetamab versus teclistamab (as detailed Section 2.10). The ITC was conducted in line with the best practices outlined in NICE TSD17 and additionally, was validated by UK clinical experts who stated that the methodology was highly robust, owing to the comparison being trial-versus-trial and additionally because the IPD was available for both trials (as discussed in Section 2.10.3).[120] Any uncertainty surrounding the base case results were explored in multiple sensitivity analyses which found the base case cost-effectiveness conclusions to be robust to uncertainty surrounding key model inputs and assumptions (as presented in Section 3.11.3).

Long-term extrapolations of the PFS, OS and TTD data from MonumenTAL-1 were required due to the median follow-up of MonumenTAL-1 being shorter than the lifetime model time horizon, which are associated with uncertainty. Moreover, owing to the OS benefit that talquetamab demonstrates compared to teclistamab (see Section 2.10.5) at the September 2024 DCO of MonumenTAL-1 in Cohort C, median OS was not reached.[119] To address this limitation, as noted in Section 3.3.2, the two-stage adjusted OS HR from the ITC of talquetamab versus teclistamab was applied to the calibrated teclistamab extrapolation in order to derive the talquetamab OS extrapolation. This approach permits the use of the trial-vs-trial ITC results, which represent the

highest grade of evidence available for assessing relative effects between talquetamab and teclistamab and leverages the approach to modelling long-term teclistamab OS that has been reviewed and agreed upon by the NICE committee as part of TA1015.[194] In addition to this, uncertainty surrounding the long-term survival estimates of talquetamab was explored by modelling individually fitted extrapolations; scenario analyses using several different individually fitted extrapolations demonstrated the base case results to be robust to variations in these estimates (Section 3.11.3).

Conclusion

Although outcomes are improving, BCMA-targeting BsAbs like teclistamab remains the only effective treatment option specifically licensed and recommended for use in TCE RRMM patients. An unmet need therefore remains for additional efficacious treatment options with alternative mechanisms of action to reduce rates of severe infections and provide patients and clinicians with the treatment choice they desire.

Talquetamab, a GPRC5D-targted BsAb therapy, has demonstrated survival advantages and a more favourable infection-related safety profile compared to BCMA-targeting BsAbs, while not compromising on patients' QoL. The with-PAS probabilistic cost-effectiveness modelling estimates presented in this submission suggest that talquetamab could increase LYs by 3.29 years and QALYs by [redacted] compared to teclistamab. This evidence further confirms the place of talquetamab as a treatment alternative to BCMA-targeted BsAbs like teclistamab for TCE RRMM patients.

Overall, considering the PAS price, the deterministic and probabilistic base case ICERs demonstrated talquetamab to be cost-effective use of NHS resources at a WTP of £30,000 for the treatment of patients with TCE RRMM.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Summary of Information for Patients (SIP)

March 2025

File name	Version	Contains confidential information	Date
ID5082_Talquetamab_NICE_SIP_noCON_17Mar2025	N/A	No	17th March 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **blue**.

1a) Name of the medicine (generic and brand name):

Generic name**: Talquetamab**

Brand name**:** TALVEY®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

This medicine is under consideration for the treatment of adult patients with **relapsed or refractory multiple myeloma (RRMM)** (defined in **Section 2a**) after at least three prior treatments, including an **immunomodulatory agent (IMiD)**, a **proteasome inhibitor (PI)**, and an **anti-CD38 monoclonal antibody (anti-CD38 mAb),** and have demonstrated disease progression on the last therapy.

IMiDs**,** PIs**,** and anti-CD38 mAbs are classes of drugs used to treat multiple myeloma. Treatments belonging to the same drug class share similarities in how they work, what they are made of and how a person's body responds to them. When a patient has received at least one treatment from **all three** of these drug classes and either their cancer has returned after a period of remission ("relapsed") or their cancer has not responded to treatment ("refractory"), they are considered to have **triple-class exposed (TCE) RRMM**. The main patient population being appraised by NICE is therefore patients

with TCE RRMM. Further details on TCE patients with RRMM are presented in **Section 2a**.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 9th October 2023, the **Medicines and Healthcare products Regulatory Agency (MHRA)** granted **marketing authorisation** for talquetamab administered **subcutaneously** (injected into the tissue between the skin and muscle), as a monotherapy for the treatment of adult patients with RRMM who have received at least three prior therapies including an IMiD agent, a PI, and an anti-CD38 mAb, and who have demonstrated disease progression on last therapy (1).

Marketing authorisation for talquetamab was granted by the **European Medicines Agency (EMA)** in the same indication on 21st August 2023 (2).

Further licensing information for talquetamab can be found on the respective websites:

- MHRA: https://products.mhra.gov.uk/search/?search=talquetamab&page=1&doc=Pil&rerouteType=0
- EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/talvey

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the

medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Johnson & Johnson Innovative Medicine (J&J IM) provided the following support to relevant patient groups in the UK in the last 12 months.

As a member of the Association of the British Pharmaceutical Industry (ABPI), J&J IM is required to publish information about relationships with patient organisations, annually, known as transfer of value (TOV) as presented in **Table 1**. Any contributions or fees shall be used exclusively as per the letter of request from the patient organisation or as outlined in the contracted service agreement, and do not obligate the patient organisation to purchase, use, recommend or arrange for the use of any product of J&J or any of its affiliates.

Table 1: Summary of support provided by J&J IM to relevant patient groups

Patient group	Engagement/activity	Reason for engagement/activity	Financial support provided
Anthony Nolan	J&J IM provided Anthony Nolan with a grant of £19,000 to support the implementation of a Cell Therapies Nurse Specialist – Year 2	Grant requested by patient organisation	£19,000
Blood Cancer UK	J&J IM covered travel costs of £371.50 for Blood Cancer UK's involvement in a J&J IM Haematology study day	Patient organisation attending J&J IM event to demonstrate resources available to HCP's and their patients	£371.50
Blood Cancer UK	J&J IM provided Blood Cancer UK with a grant of £45,910 towards the cost of delivering their National Blood Cancer Action Plan –Year 2	Grant requested by patient organisation	£45,910
Cancer 52	J&J IM provided sponsorship of £20,000 to Cancer 52 towards their activities to improve the lives of patients with less common cancers through their policy and campaigns work	Grant requested by patient organisation	£20,000
Leukaemia Care	J&J IM provided Leukaemia Care with a grant of £5000 to support the delivery of their core services including a helpline, support groups and hospital hubs	Grant requested by patient organisation	£5,000
Myeloma UK	J&J IM provided Myeloma UK with a grant of £19,400 to support the delivery of their core services including costs towards their Myeloma Info line, Ask the Nurse service, patient materials and information days	Grant requested by patient organisation	£19,400
Myeloma UK	J&J IM covered travel costs of £166.42 for Myeloma UK's involvement in an Access and	Invited to attend and contribute due to their expertise in this area	£166.42

	Reimbursement Policy Roundtable meeting.		
Myeloma UK	J&J IM provided sponsorship of £13,990 to Myeloma UK by paying the entry fee for ten of its' employees to participate in the annual fundraising Ride Myeloma 2024 event	Sponsorship fee to participate in fundraising event	£13,990
Specialised Health Care Alliance	J&J IM provided the Specialised Healthcare Alliance funding of £14,500, which was paid directly to an agency who provided secretariat support for the Specialised Healthcare Alliance, focused on policies and structures relating to NHS specialised services – 2024 programme of work	Sponsorship requested by patient group	£14,500
Specialised Health Care Alliance	J&J IM provided the Specialised Healthcare Alliance a corporate sponsorship fee of £14,500 towards 2025 work programme, which includes campaigns on policies aligned to NHS specialised services. Fee paid to agency providing secretariat support	Sponsorship requested by patient group	£14,500

Abbreviations: CAR-T: chimeric antigen receptor-T cell; HCP: healthcare professional; HTA: health technology assessment; J&J IM: Johnson & Johnson Innovative Medicine; NHS: National Health Service.

Executive Summary

Patients with TCE RRMM face a poor prognosis alongside substantial physical and psychological burden

- Multiple myeloma (MM) is a rare and incurable cancer of the plasma cells, with almost all patients experiencing a relapse or becoming refractory to treatment (3).
- Patient organisations have emphasised that, MM, particularly triple-class exposed (TCE) relapsed and/or refractory multiple myeloma (RRMM) has a significant detrimental impact on the quality of life (QoL) of both patients and caregivers (4).
- Patients with TCE RRMM experience worsening symptoms with each subsequent treatment due to the lack of response and multiple rounds of exposure (5). This translates into a need for additional care, resulting in increased burden on families and caregivers, who are simultaneously experiencing the fear and anxiety of losing their loved one (6).
- Patients and their loved ones have noted serious concerns about running out of effective therapies (4).
- The life expectancy of TCE RRMM patients reaching their 4th line of treatment was historically less than 10 months when treated with pomalidomide plus dexamethasone (PomDex) (4). However, the introduction of B cell maturation agent (BCMA)-targeting T cell redirecting (TCR) therapies within the NHS has extended median life expectancy to nearly 2 years (4).
- Despite the introduction of BCMA-targeting TCR therapies, MM remains an incurable disease.

Non-BCMA targeting, dexamethasone-free treatment options will allow personalised disease management, gains in life expectancy and reductions in the risk of severe infection

- BCMA-targeted TCR therapies are associated with a higher rate of severe infection compared with other MM therapies (7-12), which inherently has a detrimental impact on patients (4).
- With the exception of TCR therapies, all treatments currently available for TCE RRMM require concurrent treatment with steroids like dexamethasone. Patients have expressed their preference for treatment options that do not require concomitant steroid use due to the high levels of toxicity and negative impact on daily lives (4).
- Patients have expressed a desire for treatment options with flexible dosing regimens that reduce the number of hospital visits, thereby improving convenience for patients and, by extension, caregivers (13).

Talquetamab is a GPRC5D-targeting, T cell-redirecting (TCR) bispecific antibody (BsAb) that provides patients with an additional effective, dexamethasone-free treatment option.

- Similar to existing BCMA-targeting TCR therapies like teclistamab, talquetamab is a targeted immunotherapy. However, talquetamab has a novel mechanism of action, and targets the protein GPRC5D instead of BCMA.

- The clinical effectiveness and safety of talquetamab in patients with TCE RRMM was demonstrated in MonumenTAL-1, an international, multicentre, single-arm**,** open-label trial.
- The MonumenTAL-1 trial consisted of three different groups (cohorts) of patients with TCE RRMM, of which Cohort C was deemed the most representative of UK clinical practice. Patients in Cohort C had not previously received TCR therapies and received talquetamab on a biweekly dosing regimen.
- The data presented in this SIP are based on the latest published data from the 29th January data cut-off, with a median follow-up of 23.4 months (14, 15). More up-to-date, unpublished data from MonumenTAL-1 (with a longer median follow-up) are presented in the Company submission.

MonumenTAL-1 key clinical outcomes

- **Overall response rate (ORR):** Treatment with talquetamab in MonumenTAL-1 was associated with a high ORR as well as complete response or better, similar to that observed for patients receiving teclistamab in MajesTEC-1 (14-17). As ORR and response depth are linked to overall survival in RRMM, the high rates observed would typically correspond to sustained long-term survival.
- **Duration of response (DoR):** Median DoR was not reached, which means that more than half the patients with a complete response or better did not have signs of MM reappearing at the time of the latest published data (15, 18).
- **Progression-free survival (PFS):** The median PFS was 11.2 months, which means that 50% of patients receiving talquetamab every other week reached 11.2 months after their first dose of talquetamab before showing signs that their MM had progressed (15, 18).
- **Overall survival (OS):** Treatment with talquetamab resulted in 67.1% of patients in Cohort C surviving at least 2 years (15, 18). By comparison, as demonstrated in MajesTEC-1, 48.9% of patients survived at least 2 years when receiving teclistamab (17, 19).

Indirect treatment comparison of talquetamab versus teclistamab: clinical outcomes

- Patients with TCE RRMM would currently receive teclistamab as a fourth-line treatment or beyond.
- As there were no data directly comparing talquetamab and teclistamab in the same study, a robust indirect treatment comparison (ITC) was performed to compare the following outcomes: ORR, DoR, PFS and OS.
- The outcomes of the ITC demonstrated that, compared to teclistamab, talquetamab provides a statistically significantly and clinically meaningful higher ORR and OS, suggesting that talquetamab represents an efficacious treatment option for TCE RRMM patients.

MonumenTAL-1 safety outcomes

- Talquetamab was generally well tolerated by patients in the MonumenTAL-1 trial (15, 18). Side effects resulting in the need for dose reduction or discontinuation were infrequent. No treatment-related deaths occurred (15, 18).
- As previously noted, infections remain a key concern for patients with TCE RRMM. BCMA-targeting therapies can interfere with the immune system's ability to fight infection by reducing the number of patients' B cells (8, 20-22). Published literature has reported that targeting the distinct GPRC5D target is associated with longer term maintenance of immune function compared with treatments that target BCMA (23, 24).
- 70.1% of patients in MonumenTAL-1 Cohort C experienced infection, of which only 20.1% were considered to be severe (18).
- Talquetamab is also associated with GPRC5D-specific side effects; however, data from MonumenTAL-1 indicate that most were not severe and were well managed, with no related deaths (15, 18). With appropriate support measures, GPRC5D-related side effects are adequately managed, and their impact reduced (25-27).

Improved convenience for patients

- As patients can receive talquetamab via a biweekly dosing regimen, this can reduce hospital visits that may otherwise burden and inconvenience patients and their carers. This is aligned with patient sentiments expressed during the NICE appraisal for teclistamab (4).

Preservation of quality of life

- Results of MonumenTAL-1 demonstrated that treatment with talquetamab led to improvements in QoL, pain, fatigue and physical function for patients with TCE RRMM (90).
- Talquetamab is a dexamethasone-free regimen meaning patients would avoid the need for concomitant steroid use.

Conclusions

- If recommended by NICE, talquetamab would offer hope to patients with TCE RRMM.
- Talquetamab will fulfil the need for an alternative effective, dexamethasone-free treatment option that reduces the risk of severe infection over BCMA-targeting treatments, has a flexible dosing schedule and will build upon recent improvements in survival outcomes observed with other TCR treatments.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is multiple myeloma?

Multiple myeloma (MM) is a rare and incurable cancer of the **plasma cells**, a type of white blood cell that is found in the **bone marrow**. Cancerous plasma cells produce abnormal **proteins** called **M proteins**.

Most of the medical problems related to MM are caused by the build-up of these abnormal (cancerous) plasma cells in the bone marrow. This disease is referred to as MM because the cancer often affects several areas of the body, such as the legs and shoulders as well as the spine, skull, pelvis and rib cage (28).

How common is multiple myeloma?

Approximately 6,000 new MM cases are diagnosed in the UK each year, accounting for 2% of all new cancer cases from 2017 to 2019 in the UK (29). Of note, since the early 1990s, myeloma incidence rates have increased by more than a third (36%) in the UK (29).

MM more commonly occurs in people over the age of 60 years (29). It is also more common in men than women (29). Estimates in England also suggest that people with African heritage are twice as likely to get MM compared with Caucasian people (30, 31).

What is relapsed and/or refractory multiple myeloma (RRMM)?

Patients with MM will experience periods of time without symptoms followed by periods when symptoms return (**relapsed** MM). Eventually, the periods without symptoms will shorten and the illness will stop responding to the drugs given to treat it (**refractory** MM). Almost all patients with MM will experience a relapse or become refractory to treatment (32). This stage of the disease is referred to as relapsed and/or refractory multiple myeloma (RRMM).

Who are triple-class exposed (TCE) patients with RRMM?

Patients with MM usually begin treatment with drugs from three different classes. These include:

- Immunomodulatory agents (IMiDs): These work by stimulating or suppressing the immune system to target MM. These also directly attack and kill MM cells.

- Proteasome inhibitors (PIs): These work by blocking the actions of proteasomes. Proteasomes are large molecules found in all cells of the body, and these are involved in the breakdown of damaged or unwanted proteins. PIs temporarily block their function and stop them from working. This causes proteins to build up to toxic levels, killing the MM cells.

- Anti-CD38 monoclonal antibodies (mAbs): These recognise and attach to CD38 proteins found on the surface of MM cells. They directly attack and kill MM cells as well as helping the immune system to identify and kill the MM cells.

When a patient has received at least one treatment from all three classes and their cancer has returned after a period of remission ("relapsed") or their cancer has not responded to treatment ("refractory"), they are considered to have **triple-class exposed (TCE) relapsed or refractory (RR) multiple myeloma (MM)**. For simplicity, this group of patients is to as patients with **TCE RRMM** throughout the rest of this document.

Although the statistics are not well recorded, the number of patients who have TCE RRMM represents a small proportion of the overall number of patients with MM. It is estimated that 15% of MM patients in England go on to become TCE (33). Patients who require a **fourth line of treatment** are assumed to be TCE and represent approximately 684 patients in current clinical practice. This is a narrower estimate than the true number of patients who have TCE RRMM as patients may become TCE before receiving a fourth line of treatment.

What are T-cell redirecting (TCR) therapies in MM?

Since 2024, a new class of myeloma treatments known as bispecific antibodies (BsAbs) has become available in the UK. BsAbs are similar to the antibodies naturally found in blood in the sense that they bind to proteins on the surface of abnormal cells to signal them for removal. The key distinction is that BsAbs can binding to different types of cells at the same time (34).

BsAbs are part of an innovative group of therapies called T-cell redirecting (TCR) therapies, which are a form of **immunotherapy**. These therapies assist **T cells** in the immune system in recognising and killing cancerous MM cells.

What is the impact of TCE RRMM?

MM, in particular TCE RRMM, significantly impacts the QoL of both patients and caregivers. The experiences of those most affected by the condition has been extensively documented through submissions from patient organisations for various health technology assessments. These submissions highlight the considerable physical, psychological and social impact of myeloma on QoL, particularly due to the relapsing-remitting nature of the disease and patients' awareness of the limited treatment options and decreased life expectancy associated with each relapse (35).

"*Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of*

the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted. "

Patient experts have also emphasised the debilitating complications associated with the disease (36):

"*Myeloma can make you feel very isolated. The risk of infection makes you scared of going out. Especially in large groups or crowed places. I don't like going to the supermarket. I am lucky I have a car and can drive. I don't need to rely on taxis or public transport – that adds risk*."

Living with TCE RRMM can bring about many changes to daily life of patients and caregivers, which are detailed further below.

Life expectancy

The impact of MM is different for each patient, depending on several factors. These include factors such as age and gender, other medical conditions the patient may have, eligibility for **stem cell transplant (SCT)** and other disease-specific factors such as disease stage, aggressiveness and response to therapy. Historically, on average, patients with MM are expected to live for six years following initial diagnosis (37). With each subsequent therapy that patients with MM do not respond to, they are estimated to live for a shorter period of time (37).

The life expectancy of TCE RRMM patients reaching their 4th line of treatment was less than 10 months when patients were treated with PomDex (35). However, the introduction of TCR therapies within the NHS represents a step-change in management of the disease, extending median life expectancy to nearly 2 years (35).

Symptoms of TCE RRMM and their physical impact

Patients with MM experience symptoms such as weakness, fatigue and bone pain, which often result in further complications that affect day-to-day activities (38). For example, patients with MM often have imbalances in their bone cell activity, which can result in increased risk of bone fractures and development of bone disease due to the build-up of cancerous plasma cells (39). More than two thirds of all patients with MM also develop anaemia, resulting in people feeling tired and weak and making it difficult to perform everyday tasks (40).

The progression of MM to RRMM intensifies the impact of the disease, resulting in more symptoms with increased severity than those with newly diagnosed or stable MM (41). This is supported by the findings of a 2020 multicentre study on patients with MM, which found that patients with RRMM have a greater **symptomatic burden** than patients with MM.

Patients with TCE RRMM experience worsening symptoms with each subsequent treatment due to the lack of response and multiple rounds of exposure. This is in line with findings from an international study on patients with TCE RRMM, which reported that with each subsequent treatment received, people reported worsened physical functioning,

greater pain and more fatigue (5). These worsened symptoms experienced by patients with TCE RRMM have implications on their ability to perform day-to-day tasks.

Quality of life and psychological impact

In addition to the physical symptoms associated with the disease, MM also significantly impacts patients' mental and emotional health. In medicine, the physical and mental health of patients are referred to as their **health-related quality of life (HRQoL)**. HRQoL is typically measured through patient questionnaires, and scores of patients are compared with those of the general population to assess the impact of disease. In general, a higher HRQoL is beneficial and reflects a better QoL in terms of physical and mental health, and vice versa.

A diagnosis of MM causes substantial emotional distress, with patients experiencing fear due to the diagnosis and the uncertainty associated with a cancer diagnosis. Some patients describe a MM diagnosis as a 'time bomb' as they live in fear of a relapse (42). Furthermore, uncertainty about the future causes persistent anxiety and often affects patients' relationships with family and friends, who may act as informal caregivers (43, 44).

Additionally, an initial relapse in disease has been found to be associated with prolonged feelings of negative emotions such as hopelessness and resignation (43). With each subsequent relapse, patients feel more distressed and less hopeful as they may feel that available treatment options have been exhausted (43). This is particularly the case once patients become TCE. A study on patients with TCE RRMM reported that with each subsequent therapy received, patients with TCE RRMM have poorer HRQoL due to worsened physical functioning and more symptoms of pain and fatigue (5). Patients consulted by Myeloma UK during the NICE appraisal for teclistamab commented on the huge psychological impact the constant possibility of relapse has on patients (35):

"Myeloma isn't like other cancers. There isn't a tumour that can be treated and removed. You can't be cured. You need to get bloods taken every month to check for relapse. You are on continuous treatment. I am a really positive person but I get moments when I can't stop thinking about it."

Depression also affects one in four patients with MM (6). As patients with RRMM experience a greater symptomatic disease burden and are expected to live for less time than patients with MM, patients with RRMM experience worse HRQoL than patients with other cancer types (41, 45, 46). Patients consulted by Myeloma UK commented on how their condition has impacted their QoL (35):

"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."

This highlights the substantial detrimental impact RRMM, and particularly TCE RRMM, has on patients' QoL.

Impact on families and carers

Caring for a person with MM is an all-encompassing role that requires significant time for tasks such as providing help with medications, communicating with doctors and nurses, or providing support with symptoms and side effects. These responsibilities affect all aspects of the caregiver's life. The demanding nature of this role can disrupt daily routines, reduce work productivity and negatively impact the emotional well-being of caregivers. Carers often perform complicated procedures such as changing dressings or giving injections and help with other day-to-day activities (47). Carers may also accompany patients with MM to attend medical appointments, which can disrupt their employment, leading to missed work days increasing the financial impact felt by family members, who often act as informal carers (6).

The majority of carers of patients with MM are the partner or spouse of the patient, which means the impact on their QoL is anticipated to be particularly poor as they have a strong emotional attachment to the patient, and experience fear over potentially losing their loved ones (6). Symptoms of anxiety (49%) and depression (14%) experienced by partners of patients with MM further impacts the emotional impact experienced by carers (6). As mentioned previously, patients with TCE RRMM typically experience more severe symptoms which therefore would require additional care, resulting in increased burden felt by families and caregivers of patients with TCE RRMM.

The recent availability of novel therapies such as teclistamab improves the patient and carer experience and offers some relief from this burden. However, overall, the **life expectancy** for patients with TCE RRMM is still short. Patients will progress on their treatments. This leads to anxiety and emotional distress and places significant physicological burden on families and caregivers caring for patients with TCE RRMM (38). Additional treatments to prolong survival and improve QoL are therefore needed to reduce the burden of disease on patients and their caregivers.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is TCE RRMM diagnosed?

Typically, if MM is suspected, the patient will be referred to a doctor who specialises in blood disorders, known as a haematologist. A diagnosis of MM can be determined by several different tests, for example, blood tests, imaging tests and tests on samples of patients' bone marrow (48).

The diagnosis of RRMM would be informed by the aforementioned bone marrow tests and biomarkers detected in blood and, occasionally in urine, along with any signs and symptoms that may be present. Since myeloma is an heterogenous disease, a personalised treatment plan will be developed for the patient based on their test results.

When a patient has received at least one treatment from each of the classes and either relapsed or their cancer becomes refractory to treatment, they are considered to have **triple-class exposed (TCE) relapsed or refractory (RR) multiple myeloma (MM)**.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for TCE RRMM?

Treatment guidelines for the management of MM are available from the European Haematology Association and the European Society for Medical Oncology (EHA-ESMO), Internation Myeloma Working Group (IMWG), National Comprehensive Cancer Network (NCCN), British Society for Haematology (BSH) and National Institute for Health and Care Excellence (NICE) (NG35) (49-52).

The management of TCE RRMM in the UK is primarily informed by NICE guidelines for the treatment of RRMM [NG35] and published NICE technology appraisals (NICE TA1023; NICE TA970, NICE TA380, NICE TA427 and NICE TA1015) (52-57).

Current treatment pathway

Patients who are newly diagnosed with MM are initially assessed for their suitability to receive a SCT, and patients who are eligible to receive an SCT are typically treated with the following before and after receiving an SCT: daratumumab (Darzalex®) in combination with bortezomib, thalidomide and dexamethasone (58). However, not all patients are suitable for SCT due to age restrictions or additional medical complications. These patients have a limited number of treatment options available to them and typically receive daratumumab (Darzalex®) in combination with lenalidomide and dexamethasone (59). Whether a transplant or medicine is received, the first regimen a patient receives after diagnosis is considered to be their ‘first-line’ of treatment.

If and when the last line of treatment has not worked or stopped working, treatment strategy for RRMM is considered dependent on a patient's eligibility and response to previous treatment. Patients usually receive treatment from the following three drug classes in a varying order and in varying combinations: PI, IMiD, anti-CD38 mAb (60). Examples of treatments in these drug classes include but are not limited to the following:

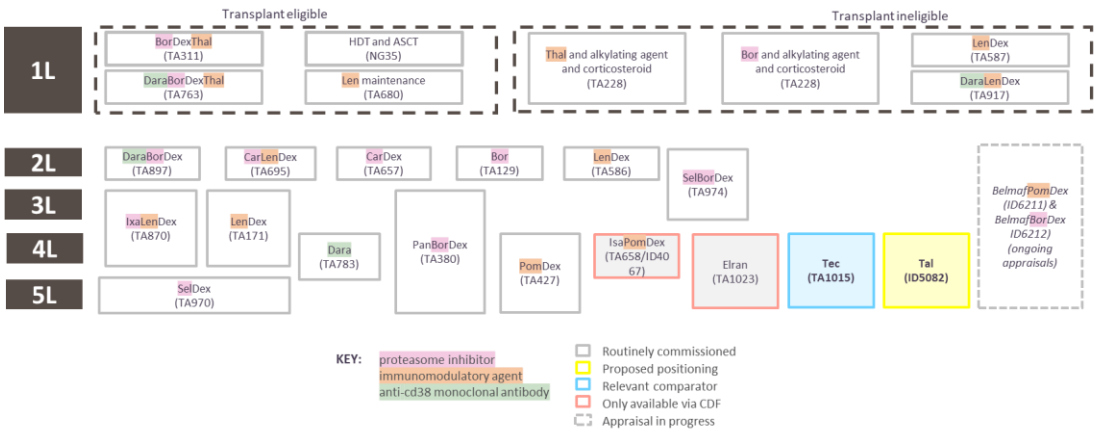
- PI: Bortezomib, carfilzomib (Kyprolis®) and ixazomib (Ninlaro®) (61)
- IMiD: Lenalidomide, pomalidomide and thalidomide (62)
- Anti-CD38 mAb: Daratumumab (Darzalex®) and isatuximab (Sarclisa®) (63)

Typically, in the treatment of MM, patients do not receive a medication from the same drug class they have previously received until all other available treatment classes have been exhausted, although there are exceptions. This approach is taken because most patients are less likely to show a good clinical response to a drug from the same class that they have previously experienced disease relapse on.

The introduction of a class of treatments called B cell maturation antigen (BCMA)-targeted bispecific antibody therapies, or 'targeted immunotherapies' has led to a substantial improvement in survival when used after the third line. Currently, there are two BCMA-targeted TCR therapies available to NHS patients, teclistamab and elranatamab. Teclistamab and elranatamab share the same mechanism of action, but the latter is currently only available via the Cancer Drugs Fund (CDF). The CDF provides temporary funding for treatments while more information on how well they work is collected (57).

The MM treatment options that a patient in the UK might receive from first-line (1L; i.e. the patient's first treatment regimen) to fifth-line (5L; i.e. the patient's fifth treatment regimen) are summarised in **Figure 1**. Of note, additional therapies with alternative mechanisms of action, which act by killing MM cells by blocking the transport of proteins needed by the cell to survive, have recently been approved for use, in particular selinexor in combination with dexamethasone at fifth-line (53, 64). BCMA-targeted bispecific immunotherapies were found to be more clinically and cost-effective treatments than selinexor and dexamethasone (35, 36).

Figure 1: The current NHS MM treatment pathway



Abbreviations: 1/2/3/4/5L: 1st/2nd/3rd/4th/5th line; ASCT: autologous stem cell transplantation; Belmaf: belantamab mafodotin; Bor: bortezomib; BsAb: bispecific antibody; Car: carfilzomib; CD38: cluster of differentiation 38; Dara: daratumumab; Dex: dexamethasone; Elran: elranatamab; HDT: high dose therapy; Isa: isatuximab; Ixa: ixazomib; Len: lenalidomide; MM: multiple myeloma; NHS: National Health Service; Pan: panobinostat: Pom: pomalidomide; PomDex: pomalidomide plus low dose dexamethasone; RRMM: relapsed/refractory multiple myeloma; Sel: Selinexor; TA: technical appraisal; TAL: talquetamab; TCE: triple-class exposed; TCR: T-cell redirecting; Tec: teclistamab; Thal: thalidomide.
Source: NICE Myeloma Diagnosis and Management (52). NICE. Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1023] (36). NICE. Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1015] (35). NICE. Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211] (65). NICE. Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212] (66).

Need for alternative efficacious treatment options

Unlike other types of cancer affecting the organs (also known as solid tumours), blood cancers cannot be managed through surgical intervention or radiation therapy. As a result, patients and treating physicians crucially rely on the availability of new treatment options to control the myeloma disease, extend survival and maintain a good QoL.

While the introduction of targeted immunotherapies is a step-change in the management of MM, patients with TCE RRMM and their treating physicians do not have access to alternative effective treatment options that prolong survival and maintain good QoL. Prior to the approval of teclistamab, patients were primarily treated with PomDex, though this treatment does not represent a viable alternative given the dramatically worse survival outcomes (patients receiving PomDex are expected to survive for approximately 9.78 months) (35). Patients interviewed by Myeloma UK as part of the NICE appraisal for teclistamab echoed this view, sharing that "*Teclistamab was my only option, I was offered palliative care quite a few times." (35).* These points clearly indicate that more treatments are urgently needed to provide greater treatment choice in the fourth-line setting.

Providing patients with treatment choice is a fundamental aspect of NHS care and service and provides patients with an increased sense of control over their disease (67, 68). Treatment choice at each stage of the treatment pathway is very important to MM patients and their loved ones, and they have voiced serious concerns about running out of effective therapies in the NHS (35). Treatment choice is particularly important in RRMM as BCMA-targeted therapies are associated with higher rates of severe infection compared with other MM therapies (7-12). This heightened risk of infection can have a highly detrimental impact on patients' QoL as they constantly fear the possibility of contracting infection. This was illustrated in the testimonials from patients with TCE RRMM who were consulted by Myeloma UK during the NICE appraisal for TA1015 (35):

"The main side effect I've experienced is infections. I get so many viruses, constant colds, sometimes more than one. My treatment has been stop, start, stop, start."

An unmet need therefore exists for TCE RRMM treatments that work a different way to provide at least equal survival benefits as BCMA-targeted therapies, while reducing the risk of severe infection and maintain QoL.

The recommendation of talquetamab for patients with TCE RRMM would address this unmet need and, most importantly, it would renew hope for patients and their families as they navigate their journey against the disease.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

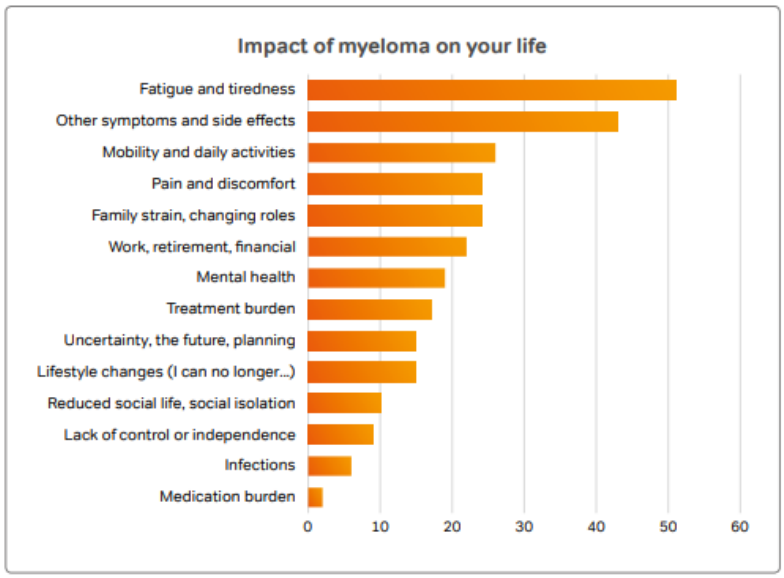
The symptoms of MM have a significant impact on a patient's QoL. There have been a number of studies aiming to understand patient preferences for treatment, including symptoms experienced and treatment benefits. However, as mentioned in **Section 2a**, given the population of patients with TCE RRMM is relatively small, there are few studies specifically in this population that report on symptoms and QoL. Hence, due to the limited number of studies for patients with TCE RRMM, studies in patients with newly diagnosed MM and RRMM have also been listed below, noting that patients with TCE RRMM experience symptoms more frequently, affecting their QoL and ability to perform day-to-day tasks (5).

Studies reporting on HRQoL

People suffering from RRMM find that their QoL can get worse over time – both because of the disease and the medicines used to treat it (69).

In 2019, NICE embarked on a research project funded by Myeloma UK to explore the quantitative methodology for eliciting patient preferences and how it could be applied in health technology assessments (HTA). The study employed robust research methodology, including a **nested survey** and a focus group consisting of 97 MM patients to understand how their disease affected their personal life (49). 'Fatigue and tiredness' were the most commonly reported challenges. Patients also described experiencing reduced independence, a change in their lifestyles and financial issues, in addition to a detrimental impact on their family and social lives.

Figure 2: The impact of myeloma on patients' lives



Source: Myeloma UK. Measuring Patient Preferences (70).

These results were also reported by patients who were consulted by Myeloma UK during the NICE appraisal for teclistamab (35):

"Myeloma has had a major impact on my QoL. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."

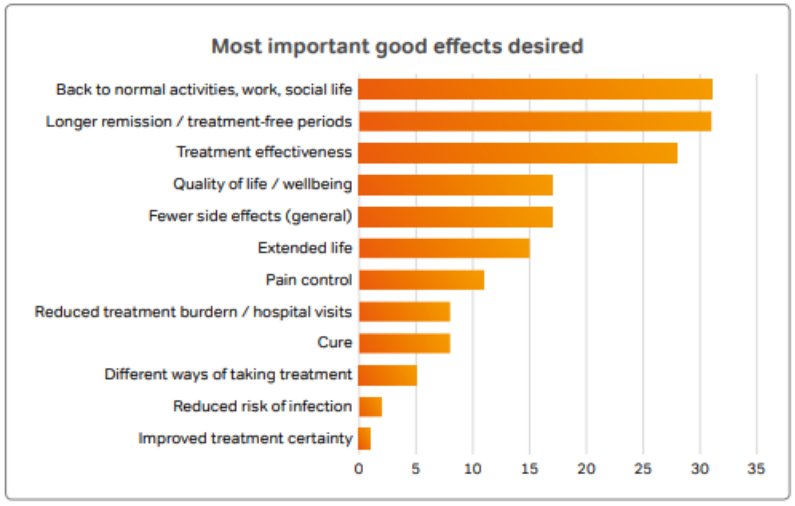
The above highlights the substantial detrimental impact RRMM, and particularly TCE RRMM has on patients' QoL, underlining that further efficacious treatments are needed to relieve the symptom and HRQoL burden imposed by the disease.

Studies reporting on treatment preference

Treatment option(s) offering longer remission

In the aforementioned 2019 survey, patients were asked about the most important positive attributes that they would want to see from their myeloma treatment. Respondents expressed a strong preference for treatments that effectively control the disease. '**Longer remission**/treatment-free periods' was the second most important attribute for treatment preference. The study also noted that carers can experience difficulties of their own, with negative repercussions for their lives (70).

Figure 3: The effects myeloma patients desire from their treatment



Source: Myeloma UK. Measuring Patient Preferences (70).

Steroid-sparing treatment option(s)

The burden of TCE RRMM on patients is further increased by the fact that all non-TCR treatments used in this setting, require concurrent treatment with the **steroid** (medicines that reduce inflammation, [i.e. swelling]) dexamethasone. Dexamethasone is associated with high levels of toxicity and therefore has a significant impact on the daily lives of patients; causing mood swings, aggression, insomnia and fatigue, which can be difficult for patients and their families to live with (71). Patients interviewed by Myeloma UK during the NICE appraisal for teclistamab expressed their preference for treatment options that do not require concomitant steroid use (35):

"I have had a lot of treatments. The worst thing I have ever had is steroids. You are up and down and up and down. You feel like you can beat the world then crash."

In summary, patient-based evidence underlines the need for additional treatment options for patients with TCE RRMM that can effectively control their symptoms and substantially improve overall survival without the need for co-administration with steroids.

Treatment option(s) that require less time in hospital

Having to attend hospital for treatment can have a substantial psychological impact on patients and it may be inconvenient for them. As such, patients value treatments that do not require them to attend hospital so frequently. Patients consulted by Myeloma UK during the NICE appraisal for teclistamab expressed their preference for treatment options that reduce the amount of time they must spend attending hospital, saying that (35):

"There are quite a few hospital visits, especially at the start".

This highlights that patients desire treatments that can be administered less frequently and more flexibly than current treatment options, which will in turn have benefits for NHS resources, as patients may not have to spend as much time in hospital.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

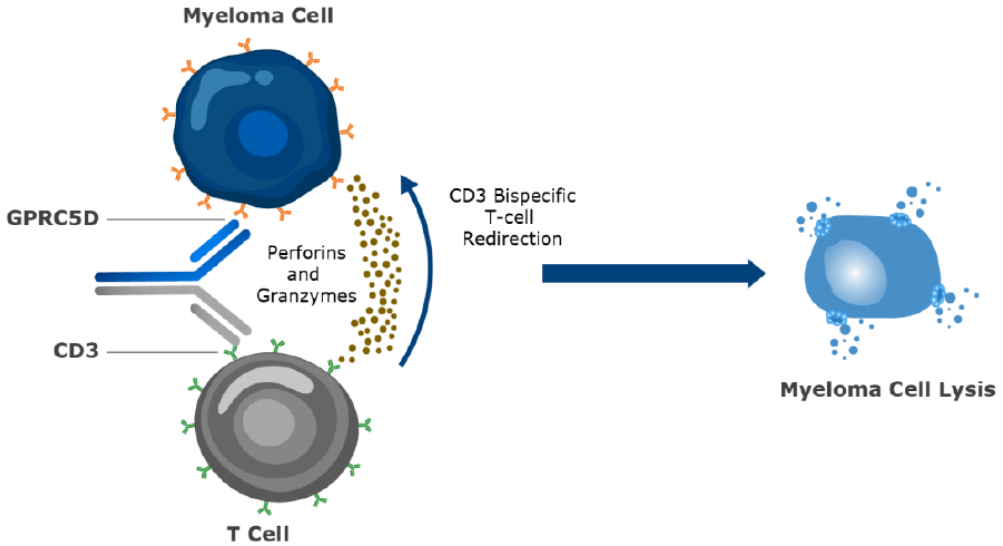
What is talquetamab and how does it work?

Talquetamab is an antibody, a type of protein that recognises and attaches specific targets in the body. It has been designed to attach to two different proteins:

- **G protein–coupled receptor class C group 5 member D (GPRC5D)**, which is found on MM cancer cells
- **Cluster of differentiation 3 (CD3)**, which is found on specific cells in the body's immune system called T cells.

When talquetamab attaches to these cells, it brings the cancer cells and T cells together. This encourages the T cells to destroy the multiple myeloma cancer cells (72). **Figure 4** below provides an overview of how talquetamab works.

Figure 4: How talquetamab works



Footnotes: Myeloma cell lysis is when the cells are killed and breakdown.
Abbreviations: GPRC5D; G protein couple receptor class 5D; CD3: cluster of differentiation 3.
Source: J&J IM. TALVEY Medical Information. (2024) (73)

Further information on how talquetamab works can be found in the patient information leaflet here: Patient Information Leaflet (Talquetamab) (74).

How is talquetamab different from existing treatment options for TCE RRMM?

Talquetamab is a targeted immunotherapy similar to teclistamab (as mentioned in **Section 2c**). While both drugs are bispecific antibodies, they target different proteins on the MM cancer cells. Teclistamab targets BCMA present on the surface of MM cancer cells, as well as CD3 receptors on T cells of the immune system. By contrast, talquetamab specifically targets GPRC5D on MM cancer cells in addition to CD3 receptors on T cells. This is a new and unique target, meaning that talquetamab is considered to be a **first-in-class** GPRC5D-targeted treatment.

Patients with MM are at increased risk of infection, and the risk of infection-related death is high (75-77). This is of particular concern for treatment with BCMA-targeting therapies, which can impair the body's ability to fight infection by disrupting the immune system (8, 20-22). With its alternative target to BCMA, talquetamab does not have the same impact on the immune system's ability to fight infection and as such, is associated with a lower rate of severe infection than BCMA-targeting therapies (78, 79). Talquetamab may therefore be more appropriate for the treatment of patients at an increased risk of infection.

In addition, as shown in **Section 3e,** data have demonstrated that overall, talquetamab showed greater overall response and survival rates compared to teclistamab. Thus, for patients with TCE RRMM, talquetamab offers the potential to be an effective alternative treatment option to currently available treatments, with potentially less concerns around infection, improving patients' overall life expectancy, while preserving their QoL.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Talquetamab does not need to be used in combination with any other treatments.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is talquetamab taken?

Talquetamab is administered by trained medical personnel as an injection under the patient's skin (subcutaneous injection) in the stomach area (abdomen) or thigh. Talquetamab is available as 2 mg/mL and 40 mg/mL solution for injection vials.

How much medicine do patients take and when?

Step-up dosing

Talquetamab can either be received on a weekly or biweekly dosing schedule. The dose will depend on the patient's body weight. A doctor will determine the **dosage and frequency** of talquetamab to be given to the patient. Treatment initiation will begin with a **step-up dosing** regimen in the first few days before reaching the 'maintenance dose'. The step-up dosing phase is described below for the weekly or bi-weekly schedule.

0.4 mg/kg once a week

- First dose received on day one: 0.01 mg/kg
- Second dose received two to four days later: 0.06 mg/kg
- Third dose received two to four days later: 0.4 mg/kg

0.8 mg/kg bi-weekly (once every two weeks)

- First dose received on day one: 0.01 mg/kg
- Second dose received two to four days later: 0.06 mg/kg
- Third dose received two to four days later: 0.4 mg/kg
- Fourth dose received two to four days later: 0.8 mg/kg

Maintenance dosing

Patients continue to receive doses of 0.4 mg/kg once every week or 0.8 mg/kg once every two weeks, known as maintenance doses, which are aimed at maintaining the benefit over the course of treatment. Patients continue to receive maintenance doses until the disease progresses or the patient experiences unacceptable toxicity.

Within the first 48 hours of the initial three or four doses of talquetamab, patients are instructed to be near a healthcare facility (i.e. hospital) and monitored for signs and symptoms such that any side effects experienced can be managed appropriately.

Further information on the administration and dosing of talquetamab can be found in the patient information leaflet (PIL) here: Patient Information Leaflet (Talquetamab) (74).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size,

comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of Talquetamab in TCE RRMM

The MonumenTAL-1 trial (NCT03399799/NCT04634552) is a **Phase I/II clinical trial** (80). The aim of the trial is to study talquetamab for the treatment of adult patients (aged ≥ 18 years old) with TCE RRMM.

The MonumenTAL-1 trial is an international, multicentre, **single-arm**, **open-label** trial. This means that all patients in the trial received talquetamab and that all patients knew they were receiving talquetamab. The first patient in the study was treated on 3rd January 2018, which corresponds to the date the first patient signed the informed consent form (79).

Based on their exposure to TCR therapies (as defined in **Section 2a**), patients with TCE RRMM can be split into two groups:

- TCR-naïve patients: These are patients who have not received TCR therapies.
- TCR-exposed patients: These are patients who have been treated with TCR therapies. The number of TCR-exposed patients in the UK is currently small but anticipated to increase, as teclistamab has recently been made available as a treatment option in the UK.

The MonumenTAL-1 trial includes three different groups (cohorts) of patients with TCE RRMM, which were divided by whether patients had received prior TCR therapies (TCR-exposed) or not (TCR-naïve) and the talquetamab dose they received:

- Cohort A: 0.4 mg/kg talquetamab once weekly, TCR-naïve
- Cohort B: Talquetamab 0.4 mg/kg once weekly or 0.8 mg/kg once every other week, TCR-exposed
- Cohort C: 0.8 mg/kg talquetamab once every other week, TCR-naïve

As most patients in Cohort B have a medical history of receiving TCR therapies that are not currently available in the UK (e.g. chimeric antigen receptor-T cell [**CAR-T**] therapies), data from this cohort are not discussed further.

Additionally, UK consultants expect that most patients will follow a biweekly (i.e., once every 2 weeks) dosing regimen of talquetamab in UK clinical practice, as receiving treatment less frequently is more convenient for patients. Therefore, only data from Cohort C of the MonumenTAL-1 trial were considered most relevant to the submission and are presented below.

The MonumenTAL-1 trial looked at how MM cells responded to talquetamab, how long patients survived on talquetamab, the optimal dosing regimen of talquetamab, how

tolerable (safe) talquetamab is, as well as the impact of treatment with talquetamab on patient HRQoL.

Data collected from Phase I of the MonumenTAL-1 trial have been reported in the publication by Chari *et al.* 2022 (81) and results from the Phase II portion of the trial were presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting by Schinke *et al.* 2023 (82), at the 2024 European Hematology Association (EHA) Congress by Rasche *et al.* 2024 (18) and at the 21st International Myeloma Society (IMS) Annual Meeting by Ye *et al.* 2024 (15).

More information about the MonumenTAL-1 trial can be found here:

- Chari *et al.* 2022 (81)
- Schinke *et al.* 2023 (82)
- Rasche *et al.* 2024 (18)
- Ye *et al.* 2024 (15)
- ClinicalTrials.gov (Study Details | A Study of Talquetamab in Participants With Relapsed or Refractory Multiple Myeloma | ClinicalTrials.gov) (80, 83)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

In the MonumenTAL-1 trial, the efficacy of talquetamab was measured by the outcomes described below (18). Data from Cohort C (talquetamab given once every 2 weeks) are presented. These are based on the latest available published data from the 29th January 2024 data cut-off, at which point patients had been followed up for a median (average) of 23.4 months. The data were presented at the 2024 EHA Congress by Rasche *et al.* 2024 (18) and at the 21st IMS Annual Meeting by Ye *et al.* 2024 (15). There are more up-to-date unpublished data from MonumenTAL-1 (with a longer median follow-up), which have been presented in the Company Submission.

Overall response rate

Overall response rate (ORR) is the proportion of people who have achieved **partial response** or better, which is measured by the amount of M proteins, a type of protein

made my MM cancer cells. A partial response means that M protein levels are at least 50% lower than before treatment (84). A **complete response** means that there are no M proteins detected in blood or urine tests and there are fewer than 5% of MM cells in the bone marrow (84).

Achieving a complete response is particularly important for patients with TCE RRMM, as attaining this level of response after having been treated with all 3 traditional classes of drugs, provides a renewed sense of hope for extended period in remission and longer lifespan as a result. Prior to the approval of BCMA-targeted immunotherapies, very few patients with RRMM achieved this level of response. In the clinical trial of PomDex (the MM-003 trial), only 7% of patients achieved a very good partial response or better (85). Similarly, in the LocoMMotion study, a **real-world evidence** study investigating the outcomes in TCE RRMM patients, only one patient (0.4%) achieved a complete response or better, highlighting how difficult it was to achieve this outcome with the previous standard of care treatments (86).

In the MajesTEC-1 trial of teclistamab, almost half (46.1%) of patients with TCE RRMM achieve a complete response or better, demonstrating the step-change in the treatment of TCE RRMM that targeted immunotherapies represent (87). The feeling of hope associated with achieving a complete response was reflected by patients receiving teclistamab who were interviewed by Myeloma UK during its' NICE appraisal (35):

"Teclistamab gave me my first complete remission… When I found out I felt relieved… It is the first time that I have felt like I don't have myeloma anymore".

In the MonumenTAL-1 trial, patients in Cohort C had a high ORR of 69.5% (18). Complete response or better was achieved by 40.3% of patients with TCE RRMM (18), a similar level to the number of patients achieving a complete response in the MajesTEC-1 trial, suggesting that patients receiving talquetamab would feel the same relief and hope that teclistamab provided. As ORR and response depth are linked with **overall survival (OS)** in RRMM, the high ORR and complete response rate observed in patients receiving talquetamab is suggested to correspond with sustained long-term survival outcomes observed in these patients (88).

Duration of response

Duration of response was measured in the MonumenTAL-1 trial as the time between patients achieving a partial response or better and signs and symptoms of MM reappearing, i.e., the length of time before the patient experiences a relapse, or death due to MM (19). Duration of response is, therefore, an important marker of how effective the treatment is by assessing how long the treatment response lasts.

In the MonumenTAL-1 trial, patients in Cohort C who experienced a response recorded a median duration of response of 17.5 months before having signs of MM reappearing (15, 18). Patients in Cohort C who had achieved a complete response or better had a longer median duration of response than patients who did not achieve this level of response (15, 18). Median duration of response had not been reached in this group, meaning more than

half the patients with a complete response or better did not have signs of MM reappearing at the time of the latest published data (15, 18).

Progression-free survival

Progression-free survival (PFS) was measured in the MonumenTAL-1 trial as the time between patients receiving their first dose of talquetamab and having signs that MM has **progressed** (refers to the worsening of the disease) or death (15, 18). In the MonumenTAL-1 trial, patients in Cohort C reached a median PFS of 11.2 months, meaning 50% of patients receiving talquetamab every other week went 11.2 months after receiving their first dose of talquetamab before showing signs that their MM had progressed (15, 18).

Overall survival

Overall survival (OS) is how long people live after receiving the first dose of treatment. MM patients and their carers place a very high value on treatments that prolong their life (89). In MonumenTAL-1, treatment with talquetamab resulted in 67.1% of patients in Cohort C surviving at least 2 years (15, 18). As demonstrated in MajesTEC-1, 48.9% of patients survived at least 2 years when receiving teclistamab (17, 19).

Indirect treatment comparison

When there are no data directly comparing two treatments in the same study, an **indirect treatment comparison (ITC)** is typically performed. This is a form of analysis where differences between the studies evaluating each of the two drugs are adjusted for, allowing their outcomes to be compared. This analysis was conducted between talquetamab in the MonumenTAL-1 trial and teclistamab in the MajesTEC-1 trial and presented in the Company Submission.

Methods

Robust statistical methods were used to adjust for the differences in patient characteristics in the MonumenTAL-1 trial and MajesTEC-1 trial. This adjustment was performed to ensure that the comparison of outcomes between talquetamab and teclistamab remained as fair as possible, with differences in outcomes being only due to the treatment received and not due to other factors. This statistical analysis is explained in further detail in the Company Submission.

Outcomes assessed

Outcomes that were investigated in the ITC include:

- ORR: This is the proportion of people who have achieved partial response or better, which is measured by the amount of M proteins, a type of protein made my MM cancer cells.

- DOR: This is the time between patients achieving a partial response or better and signs and symptoms of MM reappearing.

- PFS: This refers to the length of time between starting a cancer treatment and signs that the cancer has started to progress, or the patient's death.

- OS: This refers to how long people live after receiving treatment. OS failure was defined as death from any cause after receiving the first dose of treatment and the end of follow-up.

Results

Overall, results from the ITC demonstrated that, compared to teclistamab, talquetamab provides significantly higher ORR with similar depth and length of response, similar PFS and a significant improvement in OS.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact

In MonumenTAL-1, information was collected about the HRQoL of patients with TCE RRMM who were treated with talquetamab. These results are important, as improvements in HRQoL have been highlighted by patients as one of the most important outcomes following treatment (70).

HRQoL was measured by three questionnaires developed to assess the HRQoL of patients (90):

- The **EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L)** is a generic tool to measure how many patients experienced improvements in QoL. Patients are asked questions about whether they are experiencing problems with mobility, self-care, performing usual activities, pain and discomfort, and anxiety and depression (91)
- The **European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30)** which was used to measure how many patients experienced improvements in QoL, pain, fatigue and physical function (92)
- **Patient Global Impressions-Severity (PGIS)** is used to assess the severity of the patient's health state, on a 5-point verbal rating scale and contextualise the results of the EORTC-QLQ-C30 (93)

Results demonstrated that treatment with talquetamab led to improvements in QoL, pain, fatigue and physical function for patients with TCE RRMM (90). This result indicates that talquetamab can alleviate challenging symptoms that are most detrimental to MM patients and improve QoL in a meaningful way.

Patient preference for additional treatment options

As detailed in **Section 2c**, treatment choice is important to patients with MM and their families, and having alternative treatment options allows doctors to tailor treatment plans based on patient needs and medical history.

Improved survival

While the introduction of BCMA-targeting therapies like teclistamab has improved life expectancy and disease control, overall median life expectancy still remains ~22 months with a lack of other effective treatment options (4). Talquetamab offers patients with TCE RRMM an alternative effective treatment option to BCMA-targeting BsAb therapies.

Steroid-sparing treatment

During the teclistamab appraisal, patients reported a preference for dexamethasone-free treatment for their myeloma condition. Like teclistamab, talquetamab does not require the co-administration with dexamethasone.

Overall, this demonstrates that talquetamab represents an effective treatment alternative to teclistamab that directly addresses patient preferences for myeloma therapy, providing significant relief from their most challenging symptoms without compromising on the QoL benefits that BCMA-targeting therapies like teclistamab also provide.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

What are the side effects?

Every medicine has its own **side effects**, also known as adverse events (AEs), and the same medicine can produce different reactions in different people. Evidence for the safety

of talquetamab was collected for patients with TCE RRMM who received at least one dose of talquetamab in the MonumenTAL-1 trial (15, 18).

Very common serious side effects, which may affect more than 1 in 10 people receiving talquetamab, include (74):

- A serious immune reaction known as **immune effector cell-associated neurotoxicity syndrome (ICANS)** that may affect the nervous system and cause symptoms such as feeling confused, being less alert or aware, feeling disoriented, feeling sleepy, low energy, and difficulty thinking.
- A serious immune reaction known as **cytokine release syndrome (CRS)** that may cause symptoms such as fever, low blood pressure, chills, low level of oxygen in the blood, headache, fast heartbeat and increased level of liver enzymes in the blood.
- Low levels of a type of white blood cell (neutropenia), that helps fight infections.
- Low levels of a type of cell in your blood called platelets (thrombocytopenia), which help the blood clot.

A complete list of all potential side effects associated with talquetamab, including rare side effects, can be found in the Patient Information Leaflet (Talquetamab) (74).

Managing side-effects

The safety profile of talquetamab is considered to be manageable. Side effects experienced by patients in the MonumenTAL-1 trial were accompanied by a low rate of treatment discontinuation (15, 18), and were generally perceived as being low in severity.

Serious side effects commonly seen with other BsAb therapies (CRS, ICANS)

The side effects that occurred very commonly in patients receiving talquetamab, such as ICANS, CRS, neutropenia, and thrombocytopenia, are known to occur with other BsAb treatments for MM, including teclistamab (19). This, along with clinicians' increased experience of using targeted immunotherapies like teclistamab, means that the management of these side effects is well understood (especially for CRS and ICANS) and there are local guidance and protocols in place to deal with them when they occur.

To reduce the risk of ICANS and CRS, talquetamab is administered according to a step-up dosing schedule (**Section 3c**) and patients are given medicines before each step-dose of talquetamab that help to lower the chance of these side effects. Patients are advised to remain in close proximity to qualified treatment facilities for the first 48 hours following the step-up dosing schedule of talquetamab to monitor any signs and symptoms of ICANS and CRS (72). This ensures prompt and effective management of any side effects that arise.

Details on the management of side effects can be found in both the Summary of Product Characteristics of talquetamab, Summary of Product Characteristics (Talquetamab) and the Patient Information Leaflet (Talquetamab) (72).

Improved infection-related safety outcomes

As outlined in **Section 2c**, infections are a concern for myeloma patients and BCMA-targeting treatments are associated with a high rate of severe infections in patients, as they can interfere with the immune system's ability to fight infection by reducing the number of patients' B cells (8, 20-22). BCMA-targeting therapies may therefore be less well-suited for patients at an increased risk of death due to infection.

In MonumenTAL-1, 70.1% of patients in Cohort C experienced infection, however only 20.1% of these were considered to be severe (18). With talquetamab, given that it has a different target to BCMA, there is less impact on patients' B cells and therefore on their immune system, and consequently, the rate of severe infection is lower (24).

The management of these infections is similar for talquetamab and BCMA-targeting BsAb treatments. Clinicians can treat severe infection using intravenous immunoglobulin (IVIg), which can boost a patient's immune system, however the demand for this medicine is high and its use in the NHS is strictly constrained by the supply available (94). As talquetamab has a lower infection rate than BCMA-targeting immunotherapies, fewer patients receiving talquetamab will require IVIg to help fight their infections than patients receiving BCMA-targeting therapies (18, 19).

Overall, evidence indicates that talquetamab may lead to fewer severe infections compared to BCMA-targeted therapies, alleviating patients' concerns about the risk of infection and the social isolation they may experience because of it. Overall, evidence indicates that talquetamab may lead to fewer severe infections compared to BCMA-targeted BsAb therapies, alleviating patients' concerns about the risk of infection and the social isolation they may experience because of it. Additionally, talquetamab can also help reduce the pressure on IVIg demand associated with myeloma treatments within the NHS.

Further details on the infection-related safety outcomes with talquetamab are discussed in the Company Submission.

As talquetamab targets the protein GPRC5D, patients receiving talquetamab experienced side effects related to this target that were different to the side effects known to occur in patients receiving BCMA-targeting therapies. Very common side effects can include nail problems,and problems with the mouth such as dry mouth, distorted sense of taste or loss of taste, weight loss, dysgeusia (a change in sense of taste) as well as skin-related problems like rash. However, data from the MonumenTAL-1 trial indicated that most of these side effects were not severe and were well managed. There were no reported deaths resulting from these side effects in the MonumenTAL-1 trial.

Studies have shown that with the correct supportive measures in place, these GPRC5D-related side effects can be adequately managed, and their impact further reduced (25-27). Practical measures include the use of nystatin mouthwash or zinc and vitamin B for taste-

related side effects and the administration of topical steroids or cosmetic products such as vitamin E oil for skin and nail disorders (25-27). Dose reductions have also shown to be effective in controlling GPRC5D-related side effects in patients receiving talquetamab (25). Very few patients had to stop their talquetamab treatment due to GPRC5D-related side effects, with only 3 patients (1.9%) and 1 patient (0.6%) stopping treatment due to taste-related or skin-related side effects, respectively, showing that overall, these side effects can be controlled.

Changes in talquetamab dose received

Talquetamab was generally well tolerated by patients in the MonumenTAL-1 trial. Side effects resulting in the need for dose reduction or discontinuation were infrequent. At the time of the 29th January 2024 data cut-off in MonumenTAL-1, 15 (9.7%) patients in Cohort C had a dose reduction, while 15 (9.7%) discontinued treatment with talquetamab due to side effects (15, 18). Additionally at this data cut-off, no treatment-related deaths had occurred since the start of the study (15, 18).

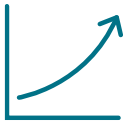
3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

The key benefits of talquetamab to patients with TCE RRMM include:

Novel mechanism of action (MoA): Talquetamab is a first-in-class GPRC5D-targeting treatment. This new MoA removes the need to re-use a treatment from the same drug class that a patient has already received. Targeting the distinct GPRC5D protein is associated with longer term maintenance of immune function compared with treatments that target BCMA (23, 24).



High overall response rates and longer life expectancy: Response is positively associated with improved survival (15, 18). Indirect evidence demonstrates that treatment with talquetamab results in higher overall response rates and prolonged life expectancy for TCE RRMM patients compared to teclistamab. If recommended, talquetamab will represent an additional effective treatment option for TCE RRMM.

Well-characterised and manageable safety profile with lower rate of infection: Talquetamab has a well-characterised safety profile that is consistent with other BCMA-targeting therapies, allowing doctors to

effectively manage side effects with routine supportive care. As a result, most patients can continue receiving treatment benefits for a prolonged duration. Importantly, the risk of infection associated with talquetamab is lower than BCMA-targeting treatments. The increased risk of severe infections has a highly detrimental impact on MM patients' QoL as they constantly fear contracting infections. Talquetamab represents an effective novel therapy associated with a lower rate of severe infections compared to BCMA-targeting therapies.

Preserved HRQoL: As a result of a high response rate and providing patients with extended periods of disease remission, talquetamab also results in meaningful improvements in QoL for patients with TCE RRMM, compared to their QoL before the start of treatment with talquetamab. Results from patient-centred evidence confirm that patients feel their symptoms are being relieved and their QoL is improving with talquetamab. TCE RRMM and its treatment not only impacts the QoL of patients but also that of their caregivers and support networks. Therefore, the benefits associated with talquetamab are likely to extend to caregivers, owing to the improvements in disease outcomes translating to a decreased level of care required.

Talquetamab does not require concurrent administration of dexamethasone. This will spare patients from the side effects commonly associated with steroids, such as insomnia and mood changes, which are known to adversely impact patients' HRQoL (95). Talquetamab will not compromise improvements in QoL achieved by teclistamab.

Flexible dosing: Patients can receive talquetamab once every other week as soon as they start treatment, meaning they do not have to attend hospital as frequently as treatments that require weekly dosing. Patients place high value on treatments that do not require them to attend hospital as frequently, as it can be a stressful experience that has a negative impact on QoL (13). The flexible dosing schedule therefore means patients receiving talquetamab can spend less time in hospital and more time with their loved ones.

Treatment choice: Treatment choice at each stage of the MM pathway is very important, as it gives patients an increased sense of control over their disease and crucially allows doctors to tailor treatment plans specific to their patients' needs and medical history (13). With its added survival benefits and manageable safety profile, talquetamab represents an effective alternative to BCMA-targeting therapies for patients with TCE RRMM, giving both patients and doctors the options they need. A

recommendation for talquetamab would renew hope for patients and their families as they navigate their RRMM journey.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration.
- What is the impact of any disadvantages highlighted compared with current treatments.

Efficacy

Similar to all existing MM treatments, talquetamab may not work for everyone and, therefore, some patients may not respond to or progress despite treatment. However, the results of the MonumenTAL-1 trial showed that almost 7 in 10 patients with TCE RRMM responded to treatment with talquetamab. Additionally, treatment with talquetamab resulted in improved survival rates when compared with teclistamab, as described in **Section 3e**.

Side effects

CRS and ICANS side effects

Serious side effects like CRS and ICANS are very common with talquetamab. However, these side effects are similarly associated with other MM treatments like high-dose therapy and stem cell transplantation (4):

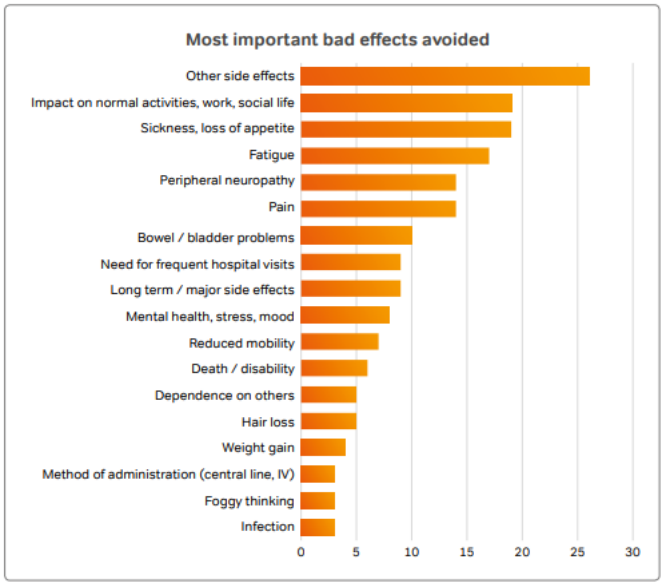
"CRS sounds awful, but it also sounds temporary. A lot easier than a stem cell transplant. With my SCT I lost my appetite and sense of taste and I love food. I was also so prone to infection I couldn't really see family and friends."

Healthcare professionals and facilities are therefore very familiar with the management of CRS and ICANS; they are equipped with the appropriate resources and training to promptly manage these serious reactions when they occur (72).

GPRC5D-related side effects

In the survey undertaken by NICE and funded by Myeloma UK, patients were asked about the most important negative attributes that they want to avoid from their myeloma treatment. Patients prefer not to have additional side effects (49).

Figure 5. The most important negative attributes patients wish to avoid with their treatment



Source: Myeloma UK. Measuring Patient Preferences (70).

As described in Section 3g, dysgeusia and weight loss are anticipated additional side effects of talquetamab as it targets GPRC5D, which is expressed on certain cells in the mouth. In MonumenTAL-1 very few patients needed to stop their talquetamab treatment due to these GPRC5D-related side effects, and no patients died due to these. Emerging studies have shown that, with the correct supportive measures in place, these GPRC5D-related side effects can be adequately managed, and their impact ameliorated (25-27).

Administration

While following the step-dosing schedule for talquetamab, patients are advised to stay close to a healthcare facility in case they experience serious side effects. This requirement for hospitalisation and specialised care during step-up phase may be viewed as a drawback of talquetamab compared to other conventional MM treatments, such as PomDex, which can be administrated in an outpatient setting. However, this inconvenience is similarly expected with other BCMA-targeted bispecific therapies currently used in UK clinical practice, and as such, it was described as “slight disadvantage” by patients consulted by Myeloma UK during the appraisals for teclistamab and elranatamab (4, 36).

As detailed in **Section 3c**, patients can receive talquetamab once every two weeks from the start of their treatment, which is not currently possible with BCMA-targeting BsAb treatments. This means patients receiving talquetamab will not have to attend hospital as much; a convenience that is highly valued by patients (13).

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects TCE RRMM

The **health economic model** was designed to represent the key features of the experience of a patient with TCE RRMM and to reflect **clinical practice** in the UK. To do this, a **partitioned survival model** was chosen, as it is a widely used tool for modelling cancer treatments. Since the MonumenTAL-1 and MajesTEC-1 trials are ongoing, the model was used to predict future survival outcomes for patients with TCE RRMM treated with talquetamab or teclistamab, based on survival equations. The model consists of three health states that a patient can be in:

- Progression-free: The patient's disease is responding to the treatment and not actively progressing to more advanced stages. This is the most desirable health state for patients.
- Progressed: The patient's cancer has worsened.
- Death.

Modelling how much talquetamab extends life

Using the model, the economic analysis considered whether and to what extent talquetamab extended patients' OS and PFS, to assess how long patients live for and how long patients live without their disease worsening, respectively.

PFS and OS derived from the ITC are the main clinical inputs that inform the economic analysis. Additional outcomes such as response rate and duration of response were not explicitly included in the model. Since the ITC was informed by detailed clinical data from the relevant trials for talquetamab and teclistamab, the model is anticipated to accurately represent the disease progression and survival rates for patients receiving these therapies in UK clinical practice.

Both the MonumenTAL-1 and MajesTEC-1 trials are ongoing, with many patients experiencing sustained overall survival; however, an economic analysis needs to capture any differences in outcomes, and therefore costs, for all patients in these trials over their lifetime. Thus, per NICE recommendations for economic modelling, the survival data for talquetamab and teclistamab were extrapolated to estimate the benefits associated with each treatment over a 40-year period (96). Equations were applied to the available survival data for teclistamab and then the differences in survival from the ITC were applied to this data to calculate the extrapolation for talquetamab.

Modelling how much talquetamab improves HRQoL

As two bispecific antibodies are compared in this economic analysis, the model assumes that patients receiving talquetamab and teclistamab would experience the same QoL in each health state. In this study, QoL was measured using a questionnaire called **European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)**, as this was the best source of robust data. The QoL measurements from the MonumenTAL-1 trial results were collected from questionnaires and converted into health 'utility' inputs to inform the economic model.

A **utility decrement** was applied to account for the differences in the side effects experienced by patients receiving talquetamab and teclistamab (as discussed in **Section 3g**).

Modelling the costs of managing TCE RRMM with talquetamab

Various costs are included in the model to capture the NHS expenditures associated with talquetamab and teclistamab in patients with TCE RRMM in UK clinical practice, allowing a comparison of these treatments. These include:

- The cost of the medicine itself and how much it costs to administer the medicine.
- The cost of starting treatment and the cost of monitoring the patients during treatment.
- The cost of side effects that happen during treatment (such as using IVIg to manage infections as described in **Section 3g**).
- The cost of subsequent treatments patients receive after disease progression, including end-of-life treatments.

Uncertainty

- Although the most recent data from the trials were used in the model, there is uncertainty around how long people would remain progression-free and alive for each treatment, as data are only available for a certain duration of follow-up. Therefore, predictions on how long people would remain progression-free and alive were used and additional scenarios in the model were explored to minimise this uncertainty.

- As both the trials informing the model (MonumenTAL-1 and MajesTEC-1) are **single-arm** trials, an ITC was needed to accurately compare talquetamab and teclistamab. The results of this comparison were used to inform the efficacy data

for each treatment in the economic analysis and ITCs using data from single-arm trials may have a risk of bias due to differences in the characteristics of patients taking part in each trial. However, in this case, as MonumenTAL-1 and MajesTEC-1 were two very similar trials, the patients taking part in each trial were very similar meaning that any bias and uncertainty is expected to be minimal.

- Most assumptions were aligned to those accepted by NICE in the teclistamab appraisal [TA1015], which could facilitate consistency in decision-making (4). Alternative assumptions have been tested in additional scenarios in the model, and the impact of these on the results is presented in Company Submission.

Benefits of talquetamab not captured in the economic analysis

Treatment with talquetamab may have many different positive impacts for patients with TCE RRMM. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured, as described below.

The value of additional treatment choice

BCMA-targeting bispecific therapies have recently been made available within the NHS to treat patients with TCE RRMM as a 4L+ treatment option (4). Treatment choice is very important to patients with MM and their families, and the lack of treatment options in the NHS is a source of anxiety that impairs patients' QoL (4, 13). The importance of treatment choice, especially at 4L+, was highlighted by patients interviewed by Myeloma UK during the NICE appraisal of teclistamab, who said that (4):

"Once you are past 4/5 lines there are less and less options" and that *"Teclistamab was [their] only option".*

The ITC results presented in **Section 3e**, show that talquetamab will improve the survival outcomes for patients with TCE RRMM compared to teclistamab, and therefore it is well positioned to be an additional effective treatment option for these patients. The recommendation of talquetamab would provide patients with the treatment choice they currently desire, which may alleviate the anxiety associated with the feeling of 'running out options' in the fourth-line setting and possibly foster a sense of hope - a value that is difficult to quantify in the economic analysis.

Opportunity to benefit from future advancements in RRMM treatment

The treatment pathway for RRMM is constantly evolving and new treatments with alternative mechanisms of action will likely be approved in the future. Owing to the increased life expectancy that it provides for patients with TCE RRMM, compared to BCMA-targeting therapies, it is possible that talquetamab may allow patients to live long enough to receive and benefit from future innovative RRMM treatments. The potential improvements in survival and QoL associated with these future treatment advances are not captured in the economic model.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Talquetamab is an innovative therapy representing a step forward in the treatment of TCE RRMM

As mentioned in **Section 3a**, talquetamab is a first-in-class treatment for TCE RRMM with a unique mechanism of action targeting GPRC5D on MM cancer cells and CD3 receptors on T cells of the immune system, which represents a key step forward in the management of MM.

As highlighted in **Section 2c**, treatment choice, and the value of hope associated with it, is extremely important to patients with MM and their families. For patients with TCE RRMM, the introduction of novel therapies like teclistamab marked a turning point in their fight against the disease, but BCMA-targeted bispecific treatments are currently their only efficacious option. Evidence indicates that talquetamab offers survival benefits over teclistamab, in addition to a reduced rate of severe infection. Therefore, the availability of talquetamab in the NHS would provide patients and clinicians with an important treatment option, even as they approach the later stages of their treatment journey.

While many new therapies have recently entered the early relapse setting, there is still a significant lack of innovation for patients with TCE RRMM. The NICE recommendation for the use of talquetamab would offer hope, and treatment choice for effective, dexamethasone-free innovative therapy that reduces the risk of severe infection and has a flexible dosing schedule.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme.

Find more general information about the Equality Act and equalities issues here.

No potential equality issues are anticipated for the use of talquetamab in adult patients with TCE RRMM.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on MM:

- Macmillan Cancer Support website: What is myeloma? | Macmillan Cancer Support
- Cancer Research UK: Myeloma | Cancer Research UK
- Myeloma UK: What is myeloma? - Myeloma UK

Further information on NICE and the role of patients:

- Public Involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs: Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/
- INAHTA: https://www.inahta.org
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: Health technology assessment: an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Anaemia	A condition where there is a reduced number of red blood cells, which may cause symptoms such as tiredness, weakness or shortness of breath
Antibody	A protein that plays an important role in the body's immune system. Each antibody is unique and recognises a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs (97)
Anti-CD38 monoclonal antibody (anti-CD38 mAb)	An antibody that binds to a protein called CD38, which is found on some blood cell types and in high levels on some cancer cells, including MM cells (97)
Antihistamines	A type of drug which helps to treat allergy symptoms
Antipyretics	A type of drug which reduces fever
B cell maturation antigen (BCMA)	A protein found on the surface of B cells of the immune system. BCMA is important in the development and survival of B cells
Biopsy	A process in which a very small part of tissue in the body is removed to look for signs of disease (98)
Bispecific antibody	A type of antibody that can bind to two different targets at the same time
Bone marrow	The spongy material found inside the centre of large bones in the body, where all blood cells are made (28)
CAR-T therapy	CAR-T therapy is a type of treatment where a patient's T cells are modified to better recognise and kill cancer cells.

Clinical practice	This refers to the treatments commonly offered to patients, often guided by clinical guidelines that provide recommendations on the use of different treatments
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease
Cluster of differentiation 3 (CD3)	A receptor found on the T cell, which is a type of white blood cell that helps the body fight infections
Complete response (CR)	The disappearance of signs of cancer in response to treatment (97). This does not mean that the cancer has been cured In the context of MM, complete response means that there are no M proteins detected in blood or urine tests and there are fewer than 5% of MM cells in the bone marrow (84)
Computerised tomography (CT)	A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. A CT scan may be used to help diagnose disease, plan treatment, or find out how well treatment is working (97)
Corticosteroids	A type of drug which reduces inflammation (i.e. swelling)
Cytokine release syndrome (CRS)	A set of symptoms that can develop as a response to infection. CRS is a type of

	aggressive immune system reaction which may be life-threatening or fatal. Symptoms of CRS include difficulty breathing, nausea, vomiting, diarrhoea, loss of appetite, fatigue, muscle pain, joint pain, swelling, low blood pressure, fast heartbeat, headache, heart, lung and kidney failure and liver injury
Disutility decrement	The reduction in HRQoL caused by a negative side effect or complication from a medical treatment. It quantifies how much a side effect negatively impacts a patient's well-being.
Dosage	Specific amount of medicine that a person should take and how often they should take it
Drug classes	Drugs in the same drug class share similarities in how they work, what they are made of and how a person's body responds to them
Duration of response (DOR)	Length of time from which patients respond to treatment until patients have signs of symptoms of cancer coming back. The definition of duration of response differs slightly for each cancer type. In MM, duration of response refers to the time between patients achieving a partial response or better and signs and symptoms of MM reappearing (i.e. the length of time before the patient experiences a relapse) or death due to MM
Dysgeusia	A condition leading to changes in the sense of taste
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial**

Elranatamab	A type of immunotherapy with a distinct target of BCMA on MM cancer cells and CD3 receptors on T cells of the immune system. By recognising these two targets, elranatamab forces the cancerous MM cells and the T cells from the body's immune system together, so that the T cell can destroy the cancer cell
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union
European Organisation for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-30)	A 30-item instrument designed to measure QoL in all cancer patients
European Quality of life-5 Dimensions-5 Levels (EQ-5D-5L)	A self-reported measure of current health covering five areas (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression) which includes five response categories
First-in-class	A drug which is the first to use a new and unique mechanism of action thereby creating a new class of medicines
Follow-up	The period of time that participants in a trial are followed up to monitor their health after they have received a treatment in a study
G protein–coupled receptor class C group 5 member D (GPRC5D)	A protein found on the surface of multiple myeloma cancer cells that is a target of talquetamab
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial

Health-related quality of life (HRQoL)	In medicine, the physical and mental health of patients are referred to as health-related quality of life (HRQoL). The HRQoL of patients are typically measured through patient questionnaires, and their scores are compared to those of the general population to assess the impact of disease. In general, a higher HRQoL is beneficial and reflects a better QoL in terms of physical and mental health, and vice versa
Immune effector cell-associated neurotoxicity syndrome (ICANS)	A serious immune reaction that may affect the nervous system and cause confusion, being less alert or aware, feeling disoriented, feeling sleepy, low energy, and difficulty thinking
Immune system	The immune system defends the body from infection. It is made up of different organs, cells, and proteins that work together
Immunoglobulins	A protein made by some types of white blood cells to help the body fight infection (97)
Immunomodulatory agent (IMiD)	A substance that simulates or suppresses the immune system and helps the body fight cancer, infection or other diseases (97)
Immunotherapy	A type of therapy that uses immunomodulatory agents (97)
Indirect treatment comparison (ITC)	A type of comparison done in evaluation of new medicines to compare the outcomes of treatments studied in different clinical trials. This type of comparison is indirect as the treatments were studied in different trials
Life expectancy	This refers to the number of years a person is expected to live

Line of treatment	This refers to the number of previous treatments a patient has received. For example, patients receiving a fourth line treatment have had three previous treatments
M proteins	An antibody found in unusually large amounts in the blood or urine of people with multiple myeloma and other types of plasma cell tumours. This is also called monoclonal protein (97)
Magnetic resonance imaging (MRI)	A procedure that uses radio waves, a powerful magnet and computer to make detailed pictures of areas inside a person's body. This can be used for diagnosis of diseases
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country
Medicines and Healthcare products Regulatory Agency (**MHRA**)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom
Multiple myeloma (MM)	MM is a rare and predominantly incurable cancer of the **plasma cells**, a type of white blood cell that is found in the **bone marrow**
Nested survey	A survey in which smaller groups of questions are included within a larger dataset, allowing for a detailed exploration of specific topics
Open-label	A type of clinical trial where participants know what treatment they receive
Overall response rate (ORR)	In the context of MM, overall response rate refers to the proportion of people who have

Overall survival (OS)	achieved partial response or better which is measured by the amount of M-proteins, a type of protein made my MM cancer cells This refers to how long people live after receiving the first dose of treatment
Partial response	In the context of MM, a partial response means that M-protein levels are at least 50% lower than it was before treatment
Partitioned survival model	A type of economic model commonly used to map the life of cancer patients. The model predicts the probability of patients staying in pre-specified states of health over a specific time period
Phase I	Clinical trials which are testing new treatments are usually into different stages, also known as phases, based on the characteristics and aims of the trial. Phase I refers to an early phase of the trial which involves a small group of participants. The main aim of a phase I trial is to find out more about the treatment and its side effects
Phase II	A clinical trial phase which involves a larger number of participants compared to a Phase I trial. The main aim of a Phase II trial is to check how much of the drug should be given, find out more about the side effects and how well the treatment works
Plasma cells	A type of white blood cell that makes large amounts of a specific antibody (97)
Positron emission tomography (PET)	A procedure in which a small amount of radioactive glucose is injected into a vein and a scanner is used to make detailed, computerised pictures of areas inside the body where glucose is taken up. As cancer cells often take up more glucose than

	normal cells, pictures can be used to find cancer cells in the body (97)
Progressed	This refers to the worsening of disease
Progression-free survival (PFS)	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse (97)
Proteasome inhibitor (PI)	These are drugs that stop the cell from breaking down any excess proteins within the cell, resulting in cell death
Protein	These are structures inside all cells that are important for many activities, including growth and repair
Refractory	Cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant during treatment
Real world evidence	Clinical data that is generated from the analysis of data in the real world, outside of a clinical trial
Relapsed	The return of a disease or the signs and symptoms of a disease after a period of improvement (97)
Relapsed or refractory multiple myeloma (RRMM)	Patients with MM will experience periods of time without symptoms followed by periods when symptoms return (**relapsed** MM). Eventually, the periods without symptoms will shorten and the illness will stop responding to the drugs given to treat it (**refractory** MM). Almost all patients with MM will experience a relapse or become refractory to treatment (3). This stage of the

	disease is referred to as relapsed or refractory multiple myeloma (RRMM)
Remission	This refers to the disease responding to treatment where signs of cancer have disappeared
Side effects	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe
Single-arm	In a single-arm trial, everyone who is enrolled in the trial receives the same treatment that is being investigated in the study
Stem cell transplant (SCT)	Stem cell is a type of cell which can develop into different types of blood cells, including red blood cells, white blood cells, blood-clotting cells (platelets). Stem cell transplant refers to the procedure by which a patient received healthy stem cells to replace their own stem cells which may have been destroyed by treatment with radiation or high doses of chemotherapy (97)
Step-up dosing	This refers to the process of slowly increasing the dosage of a drug, starting from a low dosage and building up to a higher level to minimise the incidence or risk of uncontrolled inflammatory responses leading to CRS
Subcutaneously	A type of method to inject drugs under the skin
Symptomatic burden	This refers to the collective impact of symptoms experienced associated with the disease

T cells	A type of white blood cell which helps the body fight infections
T cell-redirecting (TCR) therapies	A type of treatment using modified T cells that have been engineered to express specific T-cell receptors that can recognise and target cancer cells. This approach aims to enhance the immune system's ability to identify and destroy cancerous cells effectively
Talquetamab	A type of immunotherapy with a distinct target of GPRC5D on MM cancer cells and CD3 receptors on T cells of the immune system. By recognising these two targets, talquetamab forces the cancerous MM cells and the T cells from the body's immune system together, so that the T cell can destroy the cancer cell
Teclistamab	A type of immunotherapy with a distinct target of BCMA on MM cancer cells and CD3 receptors on T cells of the immune system. By recognising these two targets, teclistamab forces the cancerous MM cells and the T cells from the body's immune system together, so that the T cell can destroy the cancer cell
Triple-class exposed (TCE)	MM patients who have been given a proteasome inhibitor, immunomodulatory agent and an anti-CD38 monoclonal antibody as treatment
Utility decrement	Refers to a reduction in a patient's QoL due to an illness or the side effects associated with its treatment.
X-rays	A type of radiation used in the diagnosis and treatment of cancer and other diseases. When used in low doses, X-rays are used to

		diagnose diseases by making pictures of the inside of the body. In high doses, X-rays are used to treat cancer (97)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082] Clarification questions

April 2025

File name	Version	Contains confidential information	Date
ID5082 Talquetamab Clarification response_FINAL_290725_[noCON]_UPDATE	2.0	Yes	29th July 2025

Section A: Clarification on effectiveness data

Decision problem, description of the technology and clinical care pathway

A1. PRIORITY QUESTION: Please, provide the rationale for adding Minimal Residual Disease (MRD) negativity rate (which is not in the NICE final scope CS Table 1 pg. 13) to the list of outcomes to be assessed.

Many patients with MM relapse due to the residual presence of resistant plasma cells in the bone marrow, referred to as minimal residual disease (MRD), which remain even after achieving complete response (CR).[1] It therefore remains critical for more sensitive measures of response which can identify responses deeper than conventionally defined CR.[2] MRD is the most sensitive measure of response currently available and is recommended in the International Myeloma Working Group (IMWG) response assessment criteria.[2]

MRD-negativity rate, as defined in the MonumenTAL-1 trial, refers to the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} and 10^{-6} at any timepoint after initial dose of talquetamab and before disease progression or starting subsequent therapy.[3] In order to achieve MRD-negative status, patients must have less than one myeloma cell per 100,000, or 1,000,000 bone marrow cells, depending on the threshold used.[4]

MRD-negativity rate was added to the list of outcomes in the submission as it was measured in the MonumenTAL-1 trial.[5] Achieving MRD negative status is associated with substantial improvements in PFS and OS and as such is an important prognostic factor in patients with MM.[6-9] It is therefore a relevant and valuable additional clinical endpoint to assess the efficacy of talquetamab for the treatment of patients with triple-class exposed relapsed/refractory MM (TCE RRMM).[4, 5]

Summary of methodology of the relevant clinical effectiveness evidence

A2. The company's statement "*given the lower incidence of AEs in Cohort C compared with Cohort A*" (CS pg. 47) does not appear to be accurate. The rates of some AEs in Cohort C (Main document, section 2.11.2, page 115, Table 39) are

higher vs. Cohort A (Appendix L.4, page 248, Table 77). Please can you clarify the discrepancy?

- TEAEs leading to discontinuation: 9.7% vs. 5.6%
- Grade 4 AEs: 33.8% vs. 30.1%
- Grade 5 AEs: 4.5% vs. 3.5%
- TEAEs leading to death: 4.5% vs. 3.5%

J&J IM acknowledge that the number of treatment emergent adverse events (TEAEs) leading to discontinuation, Grade 4 adverse events (AEs), Grade 5 AEs and TEAEs leading to death are higher for Cohort C compared to Cohort A. However, there were fewer TEAEs related to talquetamab ([redacted]% vs. [redacted]%), serious TEAEs ([redacted]% vs. [redacted]%), serious TEAEs related to talquetamab ([redacted]% vs. [redacted]%) and Grade 1–3 TEAEs ([redacted]% vs. [redacted]%) in Cohort C compared to Cohort A.[5] Therefore, J&J IM would like to correct the statement on page 47 of the CS to reflect that the *"overall incidence of TEAEs related to talquetamab, serious TEAEs, serious TEAEs related to talquetamab and Grade 1–3 TEAEs were lower in Cohort C compared to Cohort A".*

As detailed in Section 2.3.1 of the CS, the dosing regimen of talquetamab differs between Cohorts A (0.4mg/kg weekly; QW) and C (0.8mg/kg biweekly; Q2W). Clinical feedback confirmed that the majority (90%) of patients in UK clinical practice will likely receive the Q2W regimen with the remaining 10% receiving the QW regimen, owing to the reduced requirement to attend hospital frequently and hence improved convenience over the QW regimen of Cohort A.[10] Together with clinical advice, the improved convenience of the Q2W over the QW regimen and the safety profile that is not on balance inferior to Cohort A, means that the Q2W regimen in Cohort C would be favoured in UK clinical practice and therefore, Cohort C provides the most relevant evidence for talquetamab with respect to the decision problem for the submission.

Critical appraisal of the relevant clinical effectiveness evidence

A3. CS Page 66, Table 14: Please can the company confirm that the critical appraisal tool items #11 and #12 are identical. If not, can the company please specify the difference.

The critical appraisal tool items #11 and #12 are not identical. Item 11 asks whether patients who were approached about participation in the clinical trial were representative of the target population. Item 12 asks whether the patients who said yes were representative of the target population. As such, Item 11 is about selection bias based on eligibility criteria and patient recruitment methods, whereas item 12 is about whether certain groups of patients were more likely to have been enrolled.

A4. CS Page 66, Table 14: Please, provide detailed justifications for the judgment ratings for the items #14-20 and #26-27 (for MonumenTAL-1)

14) Open label trial

15) Open label trial

16) No data dredging suspected

17) One treatment group relevant; median follow-up (and range) reported for all cohorts, and Kaplan Meier used for survival

18) Appropriate statistical analyses were used based on the study aims

19) Compliance with study drug reported in the CSR and the economic model takes this into account.

20) Outcomes were measured based on accepted and reliable methodology

26) Yes, losses to follow up were reported in the CSR.

27) Statistical power calculations described in the CSR and appropriate. The study has sufficient power to detect a clinically important effect

A5. Appendix B.1.8, Risk of bias of studies included in indirect or mixed treatment comparisons, page 119, Table 28: Please, provide detailed justifications for the judgment ratings for the items #14-20 and #26-27 (for Majes TEC-1)

Open label trial

15) Open label trial

16) No data dredging suspected

17) One treatment group relevant; median follow-up (and range) reported for whole cohort, and Kaplan Meier used for survival

18) Appropriate statistical analyses were used based on the study aims

19) Compliance with study drug reported in the CSR and the economic model takes this into account.

20) Outcomes were measured based on accepted and reliable methodology

26) Yes, losses to follow up were reported in the CSR.

27) Statistical power calculations described in the CSR and appropriate. The study has sufficient power to detect a clinically important effect.

MRD negativity rate

A6. PRIORITY QUESTION: Page 72, Table 19: Please, provide the corresponding baseline MRD negativity rates for Cohort C to gauge the percentage reduction in the MRD rate from baseline to September 2024 DCO.

As noted in the Company response to A1, MRD-negativity rate was defined in the MonumenTAL-1 trial as the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} and 10^{-6} at any timepoint after initial dose of talquetamab and before disease progression or starting subsequent therapy.[3] In order to achieve MRD-negative status, patients must have less than one myeloma cell per 100,000, or 1,000,000 bone marrow cells, depending on the threshold used.[4]

J&J IM would like to clarify that patients in MonumenTAL-1 receiving talquetamab were required to have experienced disease progression on at least three prior lines of therapy to be eligible for treatment; this means that by definition at baseline, no patients are expected to be MRD-negative.

To characterise the evolution of MRD-negativity over time, MRD-negativity rates measured at each data cut of MonumenTAL-1 were compared (Table 1). As shown in Table 1, there was a steady increase in the proportion of patients who attained MRD negativity at a rate of 10^{-5} and 10^{-6}, across the data cuts until 12.7 months of follow up, after which these levels were sustained.

Table 1. Summary of MRD-negativity rate at 10^{-5} and 10^{-6} in bone marrow at each data cut of MonumenTAL-1 (Cohort C)

Data cut	Median follow up (months)	MRD Negativity Rate (10^{-5}) [95% CI]	MRD Negativity Rate (10^{-6}) [95% CI]
May 2022 (N=145)[11]	5.1[a]	[redacted]	[redacted]
September 2022 (N=145)[12]	8.6[a]	[redacted]	[redacted]
January 2023 (N=145)[13]	12.7[a]	[redacted]	[redacted]
January 2024 (N=154)[14]	23.4[b]	[redacted]	[redacted]
September 2024 (N=154)[5]	31.2[b]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; MRD: minimal residual disease.
Source: J&J IM MonumenTAL-1 clinical study report (May 2022 DCO).[11] J&J IM MonumenTAL-1 clinical study report (September 2022 DCO).[15] Touzeau, *et al*. 2023.[13] Rasche *et al.* 2024.[14] J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[5] Rasche, et al. 2025.[16]

Subsequent treatments used in the relevant studies

A7. PRIORITY QUESTION: CS Pages 78-79: What were the exact criteria for starting the subsequent treatments in talquetamab (MonumenTAL-1) and teclistamab (Majes TEC-1) trials?

- **Was it only a progression of the disease or something else, for example other events like AEs, tolerability issues, complications?**
- **Were these criteria identical or different between the talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1) trials?**

The criteria for commencing subsequent treatment in MonumenTAL-1 is as follows:[3] *'Unless the subject is intolerant to study drug, subsequent anti-myeloma therapy cannot be started before disease progression is established per the IMWG criteria and confirmed by the sponsor. After confirmation of progressive disease, choice of subsequent therapy is at the discretion of the investigator.'*

The criteria for commencing subsequent treatment were the same in MajesTEC-1. The clinical protocol states that:[17] *'Unless the subject is intolerant to study drug, subsequent anti-myeloma therapy cannot be started before disease progression is established per the IMWG criteria and confirmed by the sponsor. After confirmation of progressive disease, choice of subsequent therapy is at the discretion of the investigator.'*

In summary, the criteria to commence subsequent therapy were the same in both MonumenTAL-1 and MajesTEC-1 trials wherein, unless study drug intolerance was demonstrated, patients must have experienced disease progression to commence subsequent treatment.

Analysis methods

A8. PRIORITY QUESTION: Weighting approaches, CS page 91: Please, provide the distribution of propensity scores and weights used in the a) ATT main ITC and b) base-case scenarios (with subsequent treatment adjusted).

The distribution of propensity scores and weights used in the ATT main ITC have been presented in Figure 16 of the CS.

J&J would like to clarify that the distribution of propensity scores and weights used in the base-case scenarios (with subsequent treatment adjusted) is the same as that of the ATT main ITC. As described in Section 2.10.4 of the CS, the subsequent treatment adjustment included a two-stage adjustment method wherein an acceleration factor was calculated to "shrink" the survival times of patients receiving non-routine subsequent treatments. As noted in the Company response to A12, this two-stage adjustment did not include any additional re-weighting via inverse probability of censoring weighting (IPCW) adjustment.

A9. Please provide a tabulation of censoring rules for PFS and OS used for the main ITC analysis separately for TAL vs. TEC study arms (ITC with all subsequent treatment effects allowed, i.e., unadjusted).

The event and censoring rules for PFS and OS for talquetamab in MonumenTAL-1 and teclistamab in MajesTEC-1 are presented in Table 2 and Table 3, respectively.

Table 2. Event and Censoring rules for PFS and OS for talquetamab in MonumenTAL-1

Situation	Time at which patient has Event or is Censored	Situation outcome
PFS		
Disease progression on study medication administration or any death	Minimum of earliest date that indicates progression and date of death	Event
No post-baseline disease assessment	Date of first dose of study medication administration	Censored
Alive and no disease progression on study medication administration	Date of last disease assessment prior to start of any subsequent anti-myeloma therapy	Censored
Withdrawal of consent to study	Date of last disease assessment prior to withdrawal of consent to study participation,[a] lost to follow-up, or start of subsequent antimyeloma therapy	Censored
Lost to follow-up		
Start of subsequent antimyeloma therapy prior to disease progression or death		
OS		
Death	Death date	Event
Patients died following consent withdrawal but with data collected as allowed by applicable regulations	Death date	Event
Patients were lost to follow-up	At the time of loss to follow-up	Censored
Patient remained alive or vital status unknown	Date the patient was last known to be alive, determined by maximum collection/assessment date	Censored

Footnotes: [a] Patients who died after consent withdrawal will be censored at the date of consent withdrawal for PFS analysis.
Abbreviations: OS: overall survival; PFS: progression-free survival.

Table 3. Event and Censoring rules for PFS and OS for teclistamab in MajesTEC-1

Situation	Time at which patient has Event or is Censored	Situation outcome
PFS		
Disease progression on study medication administration or any death	Minimum of earliest date that indicates progression and date of death	Event
No post-baseline disease assessment	Date of first dose of study medication administration	Censored
Alive and no disease progression on study medication administration	Date of last disease assessment prior to start of any subsequent antimyeloma therapy	Censored
Withdrawal of consent to study	Date of last disease assessment prior to withdrawal of consent to study participation,[a] lost to follow-up, or start of subsequent antimyeloma therapy	Censored
Lost to follow-up		
Start of subsequent antimyeloma therapy prior to disease progression or death		
OS		
Death	Death date	Event
Patients died following consent withdrawal but with data collected as allowed by applicable regulations	Death date	Event
Patients were lost to follow-up	At the time of loss to follow-up	Censored
Patient remained alive or vital status unknown	Date the patient was last known to be alive, determined by maximum collection/assessment date	Censored

Footnotes: [a] Patients who died after consent withdrawal will be censored at the date of consent withdrawal for PFS analysis.
Abbreviations: OS: overall survival; PFS: progression-free survival.

Identification of covariates

A10. PRIORITY QUESTION: CS Page 92, Table 24: 17 potential covariates were identified of which 5 were deemed to be "*priority prognostic factors*". Please, explain

- **Why were these 5 covariates prioritised?**
- **Were they used differently from other variables in the analyses?**

Please provide the data showing the prognostic strength of the 17 variables based on univariate regression analyses.

The five priority prognostic factors (i.e., refractory status, cytogenetic profile, International Staging System [ISS] Stage, time to progression on last regimen and extramedullary plasmacytoma) were prioritised based on a prognostic value assessment performed for

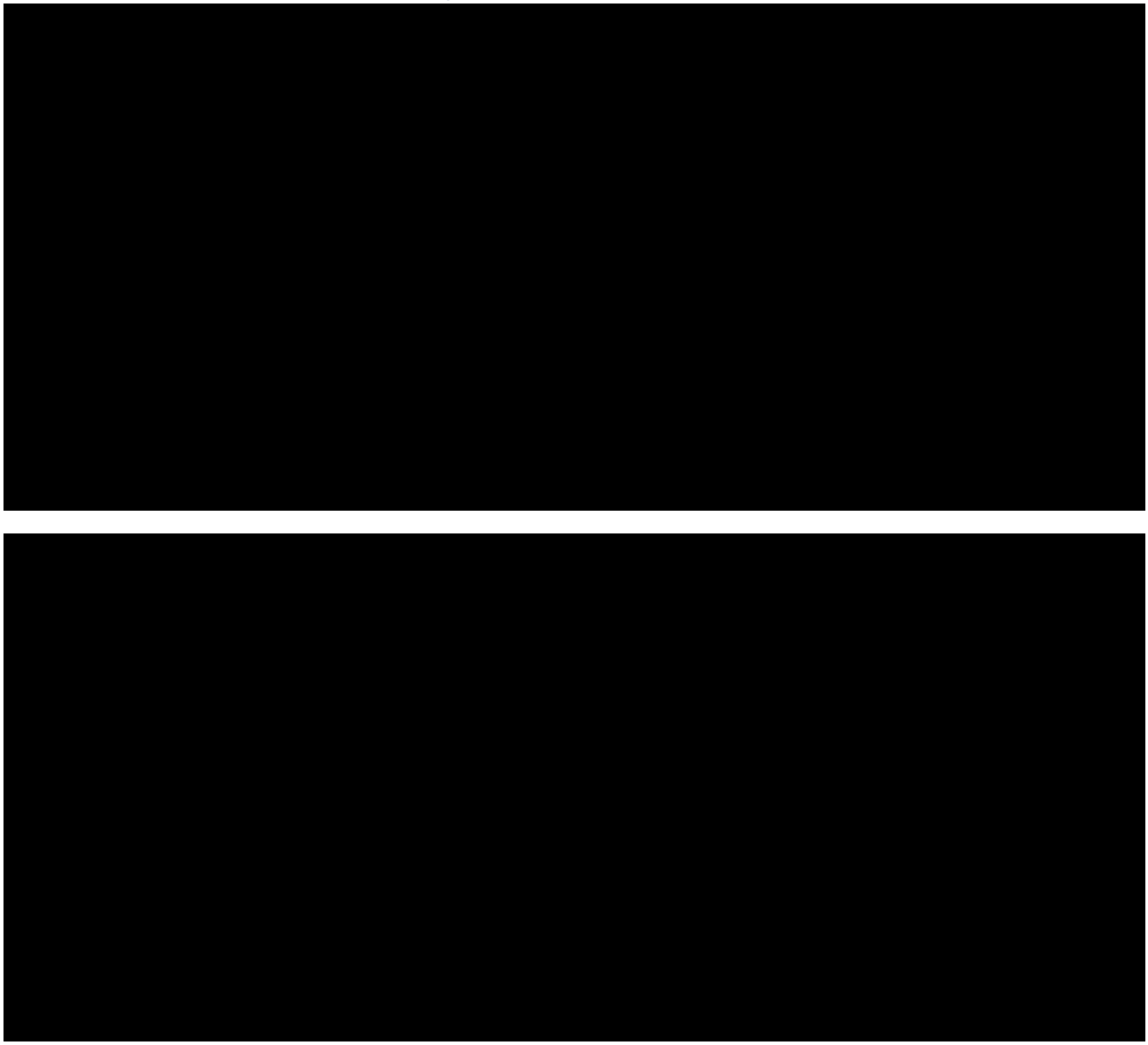
CARTITUDE-1, the pivotal trial informing the ciltacabtagene autoleucel appraisal in RRMM (TA889; terminated) and supported by the opinion of clinical experts.[18] As the patient population in CARTITUDE-1 were patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) receiving 4L+ treatment, the prognostic value assessment performed for CARTITUDE-1 remains relevant to that for the ingoing submission of 4L+ TCE RRMM patients informed by MonumenTAL-1. The assessment used an evidence-informed process that considered the prognostic strength of the factor in the efficacy outcomes and the differences across study populations. The prognostic strength of each factor for PFS or OS was assessed using univariate regression analysis in the CARTITUDE-1 ITT population. Hazard ratios and 95% confidence intervals were generated, with a hazard ratio of <1.0 indicating survival benefit. The population differences for each factor were assessed by calculating the standardised mean difference (SMDs) between the ITT (or modified ITT) populations of CARTITUDE-1 and each of the comparator studies. An SMD of 0–0.1 was considered a small difference, an SMD >0.1 to ≤0.2 was a moderate difference, and an SMD of >0.2 was a substantial difference. Given that the evidence-informed rankings were similar for PFS and OS, one list consolidating the rankings from PFS and OS was created for consistency. Clinical experts agreed on a minimum set of important factors that should be adjusted for in all analyses, which were considered 'priority' and placed at the top of the ranking list developed; this yielded the list of five prognostic factors identified above.

Four of these five priority prognostic factors (not time to progression on last regimen) were also highlighted by a recent literature review, supported by international physician consensus, as being the most important prognostic factors relevant to treatment outcomes in patients with RRMM.[19]

Whilst these five covariates were named as 'priority' covariates, J&J IM can confirm that these covariates were not used differently from the remaining 12 covariates in the ITC analyses, due to the full availability of individual patient data (IPD) from both Company-sponsored trials. This meant that all 17 covariates could be adjusted for in the ITC analyses presented in the submission.

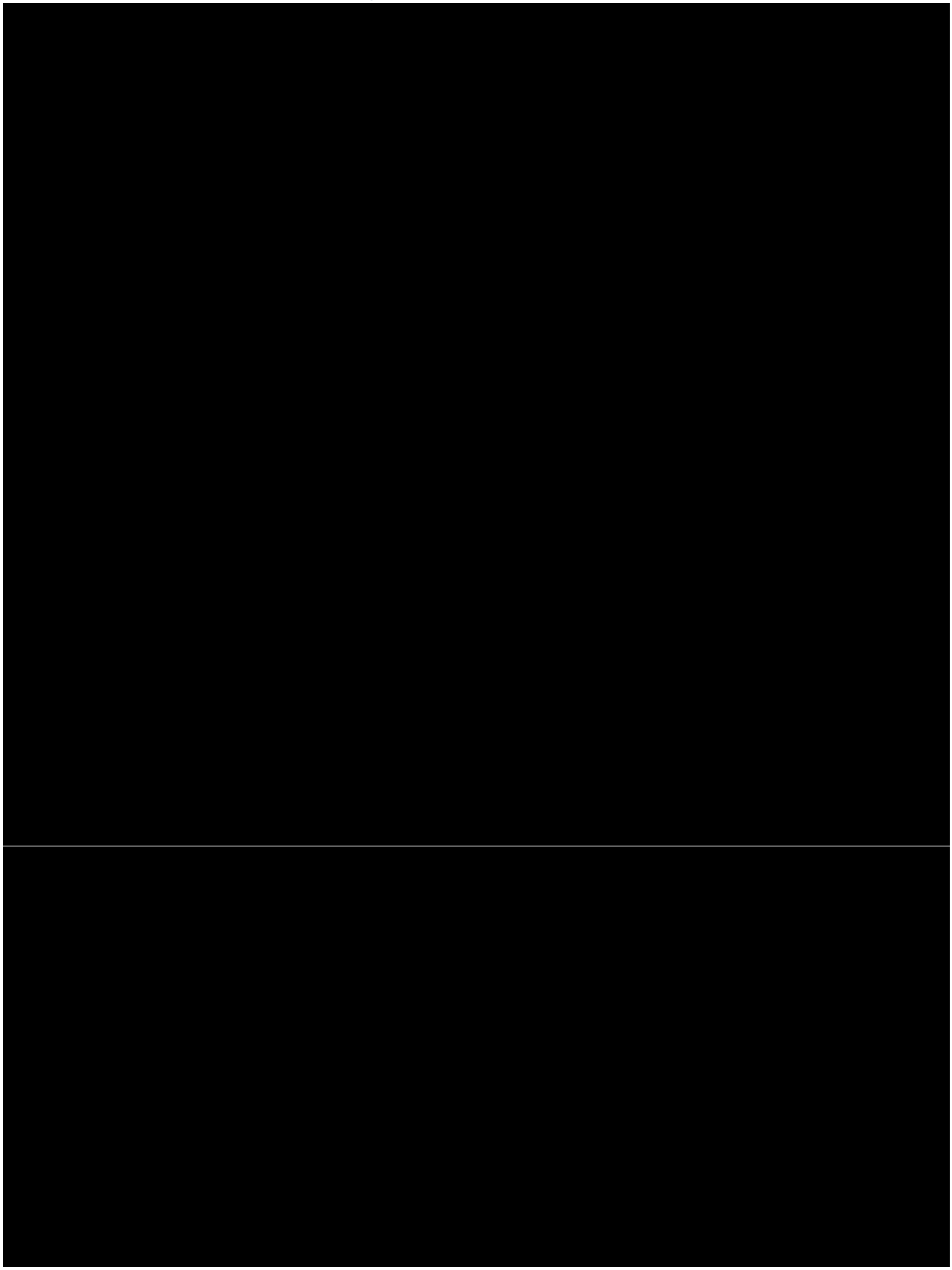
As requested by the EAG, the prognostic strength of the 17 variables for the OS and PFS comparisons based on univariate regression analyses are presented in Figure 1 and Figure 2, respectively.

Figure 1. Prognostic strength of each variable in the OS comparison between talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1)



Abbreviations: ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; IgG: immunoglobulin-G; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; OS: overall survival; SMD: standardised mean difference.

Figure 2. Prognostic strength of each variable in the PFS comparison between talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1)



Abbreviations: ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; IgG: immunoglobulin-G; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; PFS: progression-free survival; SMD: standardised mean difference.

Subsequent treatment adjustment

A11. CS Pages 99-100, Table 26: In the talquetamab trial (MonumenTAL-1), 80 patients received subsequent treatments. Please, provide the corresponding numbers for the teclistamab trial (Majes TEC-1).

A total of [redacted] patients received subsequent treatment in MajesTEC-1 (before subsequent treatment adjustment for non-routine treatments in UK clinical practice). This value refers to patients who survived progression who started at least one subsequent on or after progression date. This value is detailed in Table 26 of the CS.

A12. CS Pages 98-199, Methodology of two-stage estimation (TSE) used:

- Which accelerated failure time model was used? (Was it Weibull distribution?)
- Did the TSE include re-censoring or not?
    - If re-censoring was used, can the company please provide both results for OS (base case scenario for economic model) with and without re-censoring.
    - If re-censoring was not part of TSE, was the inverse probability of censoring weights (IPCW) used instead?
- Was the time of secondary baseline (disease progression) and time of receipt of non-UK treatment differentiated?
    - If yes, please provide the time between secondary baseline (disease progression) and time of receipt of non-UK treatment (tabular or graphical distribution) needed to evaluate whether or not the assumption of time-dependent confounding was violated.

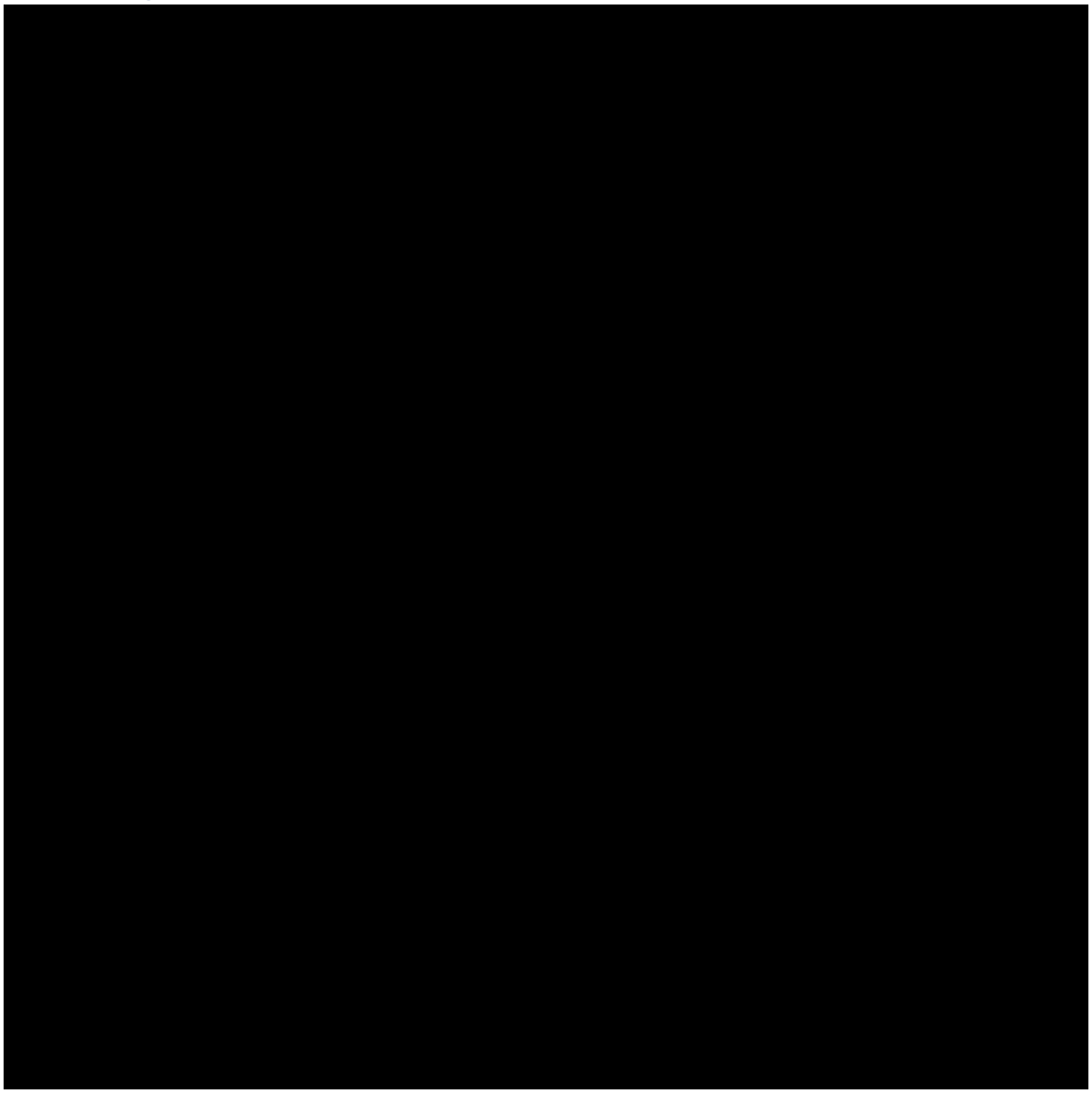
As outlined in Section 2.10.4 of the CS, an accelerated failure time (AFT) model with a Weibull distribution was used to estimate an acceleration factor. The model was adjusted using clinically relevant prognostic factors measured at the secondary baseline (or the latest assessment available prior secondary baseline) including refractory status, ISS status, extramedullary disease, cytogenetic risk, number of prior lines, years since diagnosis, age, haemoglobin, lactate dehydrogenase (LDH), Eastern Cooperativity Group Oncology (ECOG) performance status, and

time to progression in line prior switching. The resulting acceleration factor was then used to "shrink" the survival times of patients receiving non-routine subsequent treatment.

The TSE analysis did not include re-censoring as it would have caused a loss of data, and it is not recommended to be used as the default approach when the objective is to estimate long-term survival extrapolations.[20]

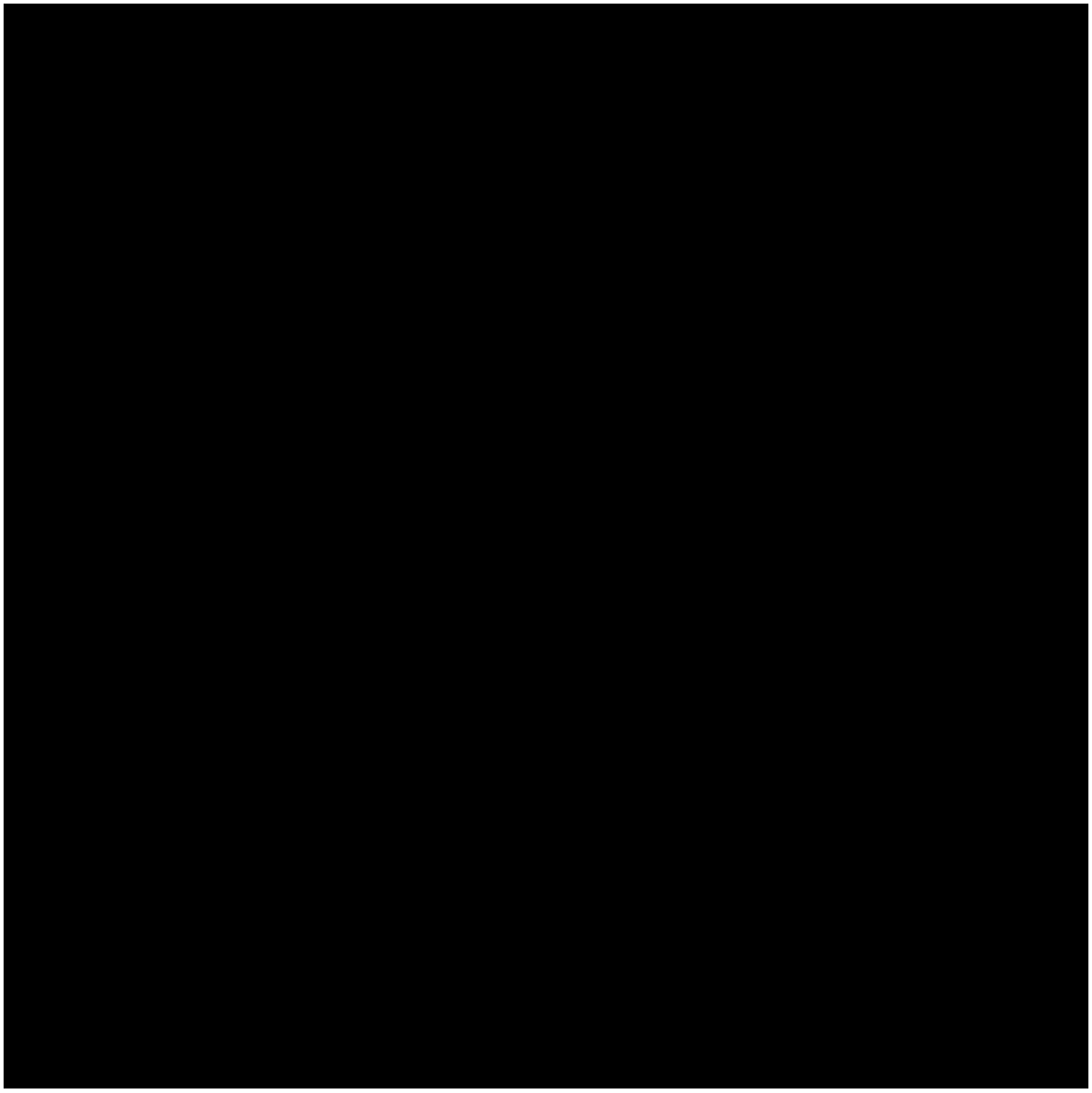
For illustrative purposes, results for the base case scenario for economic model (ATT adjusted, following subsequent treatment adjustment to reflect current UK clinical practice) are presented below without (Figure 3; hazard ratio [HR]: [redacted]; 95% CI: [redacted]) and with re-censoring (Figure 4; HR: [redacted]; 95% CI: [redacted]). The IPCW was not used to deal with potentially informative censoring as it involves increased complexity and typically produces results between the two approaches of with- and without re-censoring.[21]

Figure 3. OS Kaplan Meier (KM) curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice, without re-censoring



Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; NE: not estimable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

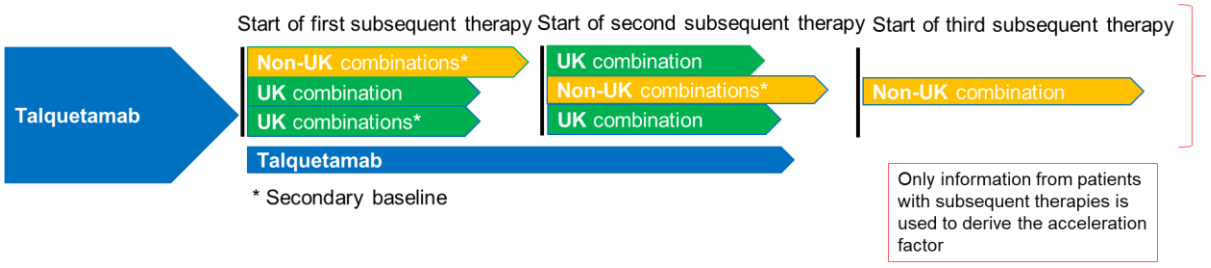
Figure 4. OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice, including re-censoring



Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; NE: not estimable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

The time of secondary baseline and the time of receipt of non-UK treatment were not differentiated. As described in NICE DSU TSD 24, a modified two-stage method was utilised in which time of treatment switch was used as a secondary baseline, rather than time to disease progression.[22] Secondary baseline was defined as the first time a patient received a non-UK relevant subsequent treatment, or the start of the first UK-only relevant subsequent therapy, rather than as disease progression. This is reflected in Figure 5 below.

Figure 5. The secondary baseline in the two-stage OS adjustment methodology



Abbreviations: OS: overall survival; UK: United Kingdom.

To control for differences between patients who switched to non-UK relevant treatment regimens and patients who switched to UK relevant regimens, prognostic factors were measured at (or the latest assessment available prior) the time of switch.

A13. CS Pages 100-101, Table 27, OS ITC analysis: the proportions of patients in both talquetamab and teclistamab arms receiving the UK treatments after subsequent treatment adjustment differ from those in CS Table 26 (pg.99).

- Were these proportions re-weighted?
    - If yes, was the IPCW used?

J&J IM would like to clarify the differences between Table 26 and Table 27 in the CS. Table 26 presents a summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1 before any subsequent treatment adjustments. The percentages listed in Table 26 have been derived by dividing n/N, where N refers to patients who survived progression who started at least one subsequent on or after progression (N=[redacted] for talquetamab [MonumenTAL-1; Cohort C] and N=[redacted] for teclistamab [MajesTEC-1]). Table 27 presents a summary of subsequent treatments received due to disease progression by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1 after non-UK subsequent treatments were removed. The following methodology was used to derive the percentages listed in the talquetamab and teclistamab arms in Table 27:

1. Treatments not available in the UK were removed from the list of subsequent treatments. The final list of subsequent treatments that were relevant to UK clinical practice reflected those used in the two-stage OS adjustment.

2. Raw percentages were then re-calculated such that total percentage of patients summed to 100%. It is important to note that following step (1), the remaining UK-relevant treatments were indirectly 'upweighted' as they represent a larger proportion of the total remaining subsequent treatment pool; this is reflected by the difference in % between Table 26 and Table 27. An IPCW approach was not used to re-weight patients.

A14. CS Pages 100-101, Table 27, OS ITC analysis: Although the subsequent non-UK treatment effects were removed/adjusted from the OS analysis, there appears to be a noticeable between-arm imbalance in the proportion of patients receiving the

same UK treatments in Table 27. Could the company please provide a rationale for this difference.

As outlined in the Company response to A13, an IPCW approach was not used to re-weight patients in the adjustment of subsequent treatments. The between-arm imbalance in proportion of patients receiving the same UK treatment following subsequent treatment adjustment is a reflection of the differences in the subsequent treatments received between the MonumenTAL-1 (Cohort C) and MajesTEC-1 treatment arms, following the adjustment method outlined in the response to A13. The subsequent treatment adjustment method does not correct for those imbalances. This also reflects anticipated UK clinical practice, in which initial therapy choice and outcome may influence the subsequent therapies that can be received by patients.

Taking all of this into account, it is clear that it would be unlikely that a between-arm balance in the proportion of patients receiving the same subsequent treatments would be observed in UK clinical practice; therefore, Table 27 in the CS is likely reflective of clinical reality in the UK

A15. PRIORITY QUESTION: CS Page 110, Table 35, OS ITC analysis: All the scenarios provided in the submission include effects of subsequent treatments available/reimbursed in the UK. Can the company provide a scenario of OS ITC estimate with all UK/non-UK subsequent treatment effects adjusted?

J&J IM acknowledges the EAG's request to provide a scenario of OS ITC estimate with all UK/non-UK subsequent treatment effects adjusted (i.e., removing the effects of all subsequent treatments). However, J&J IM does not consider the scenario informative for decision making due to (1) significant selection bias in the patient population considered in this scenario and small sample size, and (2) the requested scenario is not clinically plausible nor reflective of UK clinical practice in any way; these reasons are detailed further below.

Significant selection bias and small sample size

As outlined in Section 3.5.4 of the CS, [redacted]% of patients in MonumenTAL-1 (Cohort C) and [redacted]% of patients in MajesTEC-1 did not receive subsequent treatment following progression on talquetamab and teclistamab. Patients who did not receive subsequent treatment following progression represent patients who are not fit to receive such subsequent treatment at the time of disease progression and therefore, would subsequentially experience worse clinical outcomes and have the poorest prognosis. Applying an adjustment to remove all subsequent treatment would therefore inherently mean that the adjusted OS results would be heavily reliant on patients who have experienced the worst clinical outcomes. Due to a high level of selection bias, this would introduce substantial uncertainty in these OS results. Additionally, such an adjustment would result in reduced sample sizes, thus introducing additional uncertainty to the results.

However, for completeness and to address the EAG's request, J&J IM has provided Figure 6 below which presents the OS KM curves for talquetamab and teclistamab in patients who were alive after disease progression and did not receive subsequent treatments. Median OS for talquetamab ([redacted] months) was numerically longer than teclistamab ([redacted] months), which is indicative of a trend of improved OS in this subgroup of patients, and is directionally consistent with the OS ITC results in the overall population. As expected, the results suggest that the prognosis of this subgroup of patients is poorer than the overall patient population in the trials.

Although Figure 6 is presented below, J&J IM would like to emphasise the limitations of this analysis, specifically the significant selection bias and small sample size. Consequently, the scenario results should not be regarded as reliable or informative for decision-making purposes.

Figure 6. OS KM curves for talquetamab and teclistamab in patients who were alive after disease progression and did not receive subsequent treatments

Abbreviations: OS: overall survival; PD: progressed disease; PFS: progression-free survival; TAL: talquetamab; TEC: teclistamab.

Clinical implausibility and not reflective of UK clinical practice

Moreover, given that the receipt of subsequent treatment represents a mainstay in the MM treatment pathway and most patients would be fit enough to receive subsequent treatment, removing all subsequent treatments would not accurately represent clinical practice. Indeed, as accepted by the NICE committee in TA1015, [redacted]% of patients receiving teclistamab were assumed to receive subsequent treatment (based on MajesTEC-1).[23] In addition to this, MM is a predominantly incurable, relapsing disease with no current cure.[24] It is therefore crucial in the TCE RRMM disease setting that patients receive subsequent therapies in order to extend their lives. Therefore, bearing in mind that a high proportion of patients receiving subsequent treatment would similarly be anticipated in UK clinical practice, any scenario modelling 0% of patients receiving subsequent treatment would be completely implausible and associated with substantial generalisability concerns to UK clinical practice.

Therefore, for the reasons outlined above, while J&J IM has provided OS KM curves where all UK/non-UK subsequent treatment effects have been removed (Figure 6), **J&J IM would like to emphasise that the results are associated with considerable uncertainty and are not reflective of clinical reality. As such J&J IM does not consider it to be informative for decision making.**

Alternative scenario analyses

As presented in Section 2.10.4–2.10.5 of the CS, J&J IM have provided more informative scenario analyses to account for any uncertainty with the base case ITC approach (in which patients receiving subsequent talquetamab following teclistamab treatment were not included as this does not reflect current UK clinical practice). These included the "All-Out" scenario in which patients receiving subsequent teclistamab and talquetamab in MonumenTAL-1 and MajesTEC-1 were removed and the "All-In" scenario in which both teclistamab and talquetamab could be received as subsequent therapies. The results of these scenario analyses were consistent with the base case ITC analysis therefore demonstrating the robustness of the base case results, with talquetamab demonstrating a significant OS benefit over teclistamab.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. PRIORITY QUESTION: Please clarify the use of hazard ratios employed in the development of the base-case model for talquetamab PFS and for talquetamab OS.

In particular: please state the HR values used and their source together with the parametric model* to which they have been applied (to the time point over which they operate). It would help EAG if this was done by populating the Table below. Please do not reply by referring to economic model or submission figures.

* Please provide a plot for this model.

As detailed in Section 3.3.2–3.3.3 of the CS, the proportional hazards (PH) assumption was assessed to determine the most appropriate approach to model PFS and OS for talquetamab. Based on the assessment of the log-cumulative hazard plot for talquetamab and teclistamab (wherein the plot was predominantly parallel; Figure 25 of the CS) and Schoenfeld residual plot (wherein the plot was horizontal with a p-value of >0.05), there was no evidence to reject the PH assumption between talquetamab and teclistamab for both OS and PFS.

In the recent NICE evaluation of the teclistamab in TA1015, the calibrated LogNormal curve was selected for both PFS and OS and accepted by the NICE committee.[23] Given that the PH assumption was not violated, the use of a hazard ratio (HR) approach to derive the talquetamab OS and PFS extrapolations was considered the most robust approach, presenting the least amount of uncertainty. The approach permits the use of the trial-versus-trial ITC results comparing talquetamab and teclistamab, which represented the highest grade of indirect evidence available to assess the comparative efficacy of the two treatments.

Consequently, as detailed in Table 4 below, the HRs for OS (following two stage adjustment to remove the effects of subsequent treatments that are not routine UK clinical practice) and PFS were applied to the LogNormal ATT-adjusted OS and PFS extrapolations for teclistamab,

calibrated in line with the accepted approach in TA1015.[23] Full details on the Committee-accepted survival extrapolations of teclistamab in TA1015 are provided in Appendix A.

Table 4. Hazard ratios used for OS and PFS

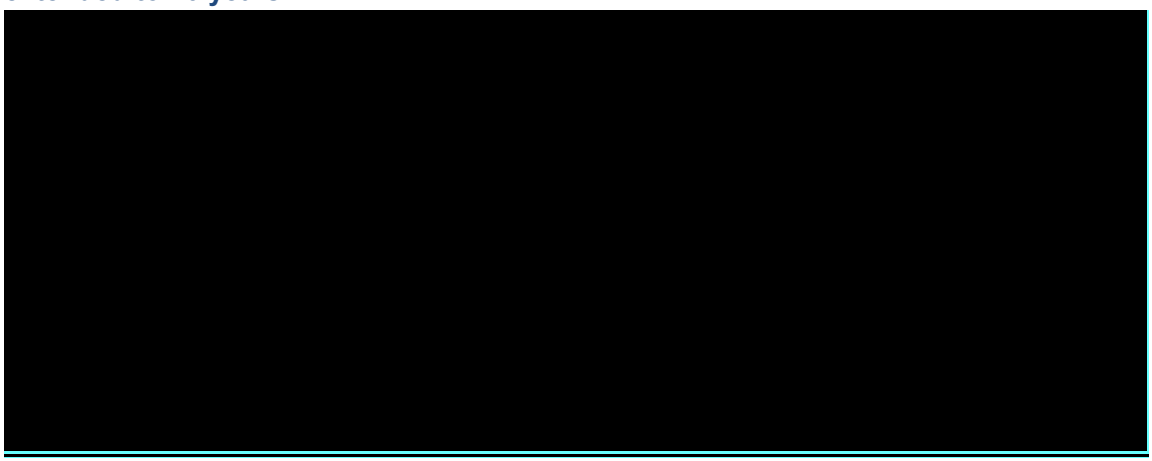
Overall survival		
HR value used	**Source of HR**	**Model to which HR was applied**
[redacted] (95% CI: [redacted]	The base case ITC comparing talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1), which is following the two-stage adjustment to reflect current UK clinical practice	Figure 7: LogNormal ATT-adjusted OS extrapolation for teclistamab (MajeTEC-1) following subsequent treatment adjustment, calibrated using accepted approach in TA1015 [redacted] **Abbreviations:** KM: Kaplan-Meier; OS: overall survival.
Progression free survival		
HR value used	**Source of HR**	**Model to which HR was applied**
[redacted] (95% CI: [redacted]	The ITC comparing talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1)	Figure 8: LogNormal ATT-adjusted PFS extrapolation for teclistamab (MajeTEC-1) calibrated using accepted approach in TA1015 [redacted] **Abbreviations:** KM: Kaplan-Meier; PFS: progression-free survival.

B2. Submission Figure 27 is titled: **Talquetamab and teclistamab OS extrapolation, post two-stage adjustment**, and the graph extends to 15 years. The economic model is set to 40 years.

A] **PRIORITY QUESTION**: **Please supply a graph showing the economic base-case OS models for talquetamab and for teclistamab that extends to the full 40-year time horizon (please do not refer EAG to figures in the economic model or in the submission).**

The requested figure showing the OS extrapolations for talquetamab and teclistamab, post two-stage adjustment, extended for 40 years is provided in Figure 9.

Figure 9. Talquetamab and teclistamab OS extrapolation, post two-stage adjustment, extended to 40 years



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

B] Please clarify the method used to extend the model lines seen in Figure 27 to the 40-year time horizon OS for each arm in the base-case.

To clarify, the HR of [redacted] was applied to the teclistamab extrapolation shown in Table 4 for the full length of the 40 year model time horizon, in the same way as described in response to clarification question B1. The extrapolation accounts for general population mortality (GPM).

C] Please confirm that the model line for talquetamab in Figure 27 is derived by applying a hazard ratio of [redacted] to the teclistamab model line.

Yes, J&J IM can confirm that this is correct. The talquetamab OS curve is modelled over time by applying an OS HR of talquetamab vs. teclistamab (HR: [redacted], 95% CI: [redacted]) to teclistamab OS curve.[23]

D] **PRIORITY QUESTION**: **Figure 27 shows Kaplan-Meier plots labelled talquetamab and teclistamab. Please identify which, if any, of the Kaplan-Meier plots shown in Figures 10, 20, 21, 23, and 27 correspond to those depicted in Figure 27**.

The Kaplan-Meier plot shown in Figure 21 of the CS correspond to those depicted in Figure 27, as this plot shows the OS for talquetamab and teclistamab, following ATT-weighting and the two-stage subsequent treatment adjustment to reflect current UK clinical practice.

B3. PRIORITY QUESTION: Please provide justification for applying an AFT-model-only (log-normal) in a setting where a time-constant hazards ratio approach is used?

J&J would like to highlight the importance of distinguishing between the use of a **hazard ratio** (HR) versus the **baseline hazard** associated with log-normal (or any other extrapolation), as these represent two distinct factors.

The HR between talquetamab and teclistamab, estimated using a Cox proportional hazard (PH) model, does not specify the baseline hazard. This baseline hazard can take any shape, as long as it is non-negative. The estimated HR was subsequently applied to the teclistamab OS curve, which had been calibrated based on the approach which was validated and accepted by the NICE committee as part of TA1015.[23] This calibration approach is described in further detail in Appendix A below.

The appropriateness of applying the HR estimated using the Cox PH model does not rely on the accelerated failure time (AFT) property of the LogNormal model. The only relevant consideration is whether the PH assumption is suitable or violated. As the AFT property of the LogNormal extrapolation is not relevant in this context, the HR estimated from the Cox PH model could have been applied to a survival curve with any hazard pattern as long as the PH assumption holds.

As detailed in Section 3.3 of the CS, there is no evidence that the PH assumption should be rejected based on the log-cumulative hazard plots and Schoenfeld residual plots for talquetamab and teclistamab (for OS [post two-stage adjustment], PFS and TTD). As the PH assumption holds for each endpoint, and the corresponding calibrated curves for teclistamab were validated and accepted by NICE as part of TA1015, the Cox PH model approach was considered valid.

When a HR is applied to survival curves which have been modelled in line with LogNormal (or LogLogistic or Generalised Gamma), the HR becomes a multiplication factor that is applied to the estimated survival probabilities. This is conceptually different from having two treatment arms following the same parametric distribution, but nevertheless represents a methodologically appropriate means for modelling the comparative efficacy between two treatments.

B4. Please provide further details on how the attenuation factor was derived, and whether alternative calibration approaches were considered?

In line with TA1015 and the approach accepted by NICE as part of that appraisal, the attenuation factor for teclistamab was derived using a standardised mortality ratio factor applied to the general population mortality.[23]

OS and PFS per cycle hazards beyond 5 years were modified in order to match the long-term OS and PFS estimates of teclistamab with the clinical expert input in TA1015. The adjustment started after year 5 given it is expected that the survival trend would not change immediately after the end of the follow-up in the MajesTEC-1 study (median follow-up of 30.4 months).[25]

Beyond 5 years, the per cycle OS hazard from the original model was replaced by general population mortality per cycle between year 5 to year 10, multiplied by a constant so that the cumulative hazard at year 10 results in the 10-year survival estimate provided by clinical expert opinion (10%; mid-point of clinical expert estimate). The same method is used between years 10 and 15: the general population mortality between year 10 and 15 was multiplied by a different

constant so that the cumulative hazard at year 15 results in the survival estimate provided by clinical expert opinion for year 15 (3%; mid-point of clinical expert estimate).

The constant used between years 5 and 10 was [redacted] which was calculated by dividing the difference of cumulative hazard needed to reach 10% survival at 10 years (e.g. [redacted]) and the cumulative hazard at the time of start of OS hazard adjustment ([redacted]) by the sum of the general population mortality per cycle during this period ([redacted]). The constant used between years 10 and 15 was [redacted] which was calculated by dividing the difference of cumulative hazard needed to reach 3% survival at 15 years [redacted] and the cumulative hazard at year 10 ([redacted]) by the sum of the general population mortality per cycle during this period ([redacted]).

PFS was adjusted using the same adjustment start time (5 years) and method as described above for OS estimates. However, instead of using the general population mortality as a reference, the per cycle hazard from the original PFS extrapolation was used to calculate the constant in the first period (i.e., year 5 to year 10; [redacted]) and the second period ([redacted]). The cumulative PFS hazard at 5 years was [redacted].

TTD was adjusted similarly in line with the methods described for PFS and OS above. The per cycle hazard from the original TTD extrapolation was used to calculate the constant in the first period (i.e., year 5 to year 10; [redacted]) and the second period (i.e., year 10 to year 15; [redacted]). The cumulative PFS hazard at 5 years was [redacted]. The calibration approaches described for OS, PFS and TTD ensured that the long-term extrapolations for teclistamab were consistent with clinical expert estimates, and was accepted by the NICE committee in TA1015.[23]

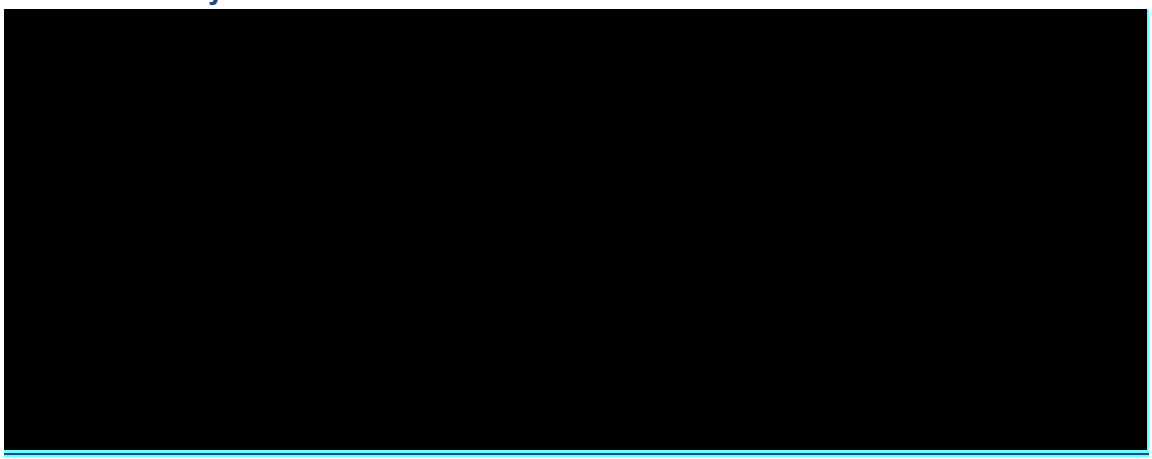
This approach to derive the attenuation factor was considered appropriate as it enabled the inclusion of data from both MonumenTAL-1 and MajesTEC-1 within their follow-up periods. This approach was also consistent with that accepted by NICE in TA1015.[23] Consequently, the approach provided the most robust evidence for the comparison of talquetamab and teclistamab and alternative approaches were not considered.

B5. Submission Figure 30 is titled **Talquetamab and teclistamab PFS extrapolation**. This graph extends to 10 years.

A] **PRIORITY QUESTION**: **Please supply a graph that shows the economic base-case models for PFS for each arm that extends to the time horizon of 40 years (please code the plot lines so that overlap can clearly be distinguished; please do not refer EAG to a graph in the economic model).**

Figure 10 shows the PFS extrapolation for talquetamab and teclistamab, over the full 40-year model time horizon. As the PFS HR is close to 1 ([redacted] [95% CI: [redacted], [redacted]]), the extrapolations for teclistamab and talquetamab remain together throughout the extrapolated time horizon. As requested, the extrapolations have been coded such that the overlap can be better distinguished; this has been done through use of dotted lines.

Figure 10. Talquetamab and teclistamab PFS extrapolation, post two-stage adjustment, extended to 40 years



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

B] **PRIORITY QUESTION**: **The derivation of the teclistamab model line is described as: *"following the accepted approach in TA1015".* Please describe this approach in full. In view of time scales the EAG do not wish to navigate more than 300 pages of committee papers to extract this information.**

The full details of the PFS extrapolation approach for teclistamab that was accepted in TA1015 are provided in Appendix A.[23]

C] Please clarify the hazard ratio used to derive the talquetamab PFS plot line (Figure 30) and which teclistamab model line this was applied to (please cross check this against response to clarification question 1).

A hazard ratio of [redacted] from the ITC comparing talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1) was used to derive the talquetamab PFS extrapolation from the LogNormal ATT-adjusted extrapolation for teclistamab, calibrated in line with the approach that was accepted in TA1015.[23]

B6. PRIORITY QUESTION: **Time to treatment discontinuation of teclistamab is described as *"following the accepted approach in TA1015".* Please describe this approach in full. In view of time scales the EAG do not wish to navigate more than 300 pages of committee papers to extract this information**.

The full details of the time to treatment discontinuation (TTD) extrapolation approach for teclistamab that was accepted in TA1015 are provided in Appendix A.[23]

B7. PRIORITY QUESTION: **For all Kaplan-Meir plots in the submission please supply the number of events and the number of censorings.**

As agreed upon with the EAG during the clarification meeting, only the KM plots for key clinical endpoints (OS, PFS and TTD), with the number of events and censorings, at 3-month intervals are provided below. A summary of corresponding CS figures is outlined below for clarity:

Overall survival

- Figure 11 is the equivalent of Figure 10 from the CS
- Figure 12 is the equivalent of Figure 22 from the CS
- Figure 13 is the equivalent of Figure 23 from the CS
- Figure 14 is the equivalent of Figure 24 from the CS

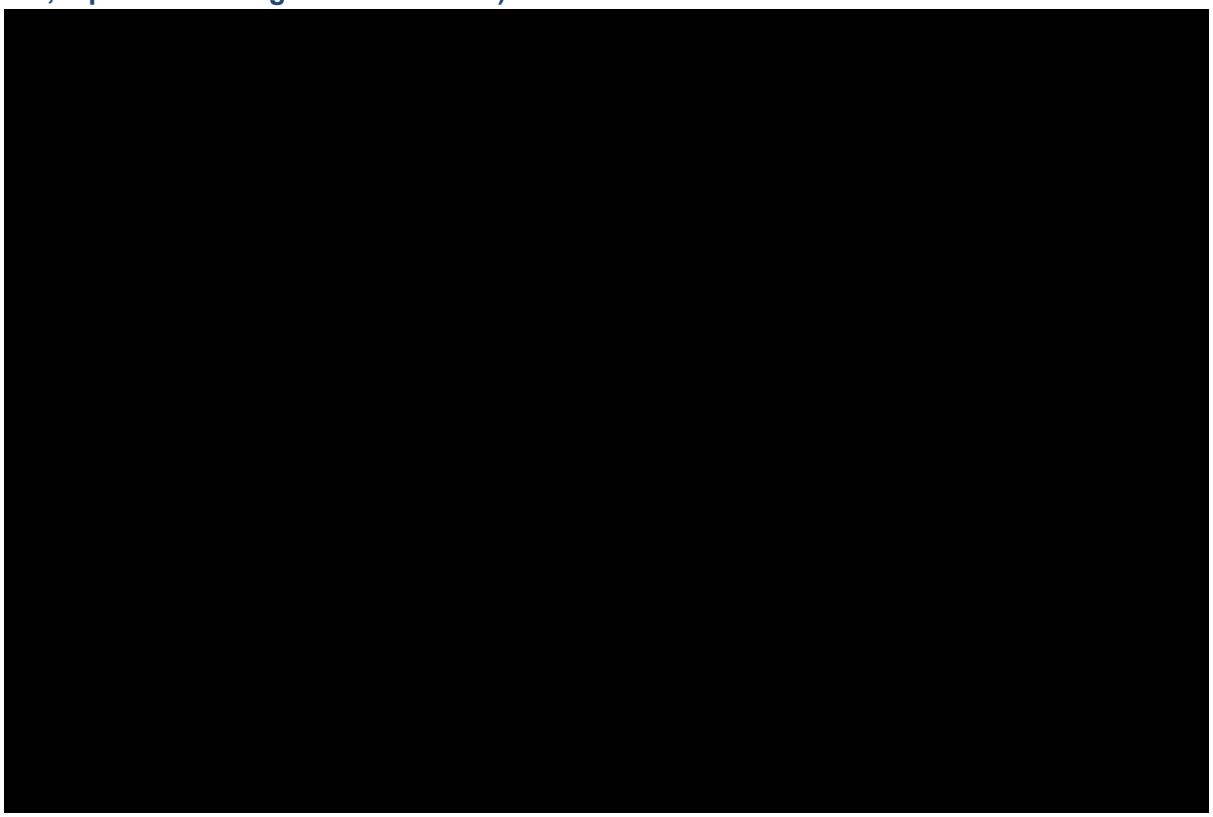
Progression-free survival

- Figure 19 of the CS already includes the numbers of events and censorings for Cohort C of MonumenTAL-1 and therefore has not been reproduced here

Time to treatment discontinuation

- Figure 15 corresponds to the KM data informing Figure 33 from the CS

Figure 11. KM plot for overall survival; Cohort C (0.8 mg/kg Q2W) (September 2024 data cut; equivalent of Figure 10 in the CS)



Footnotes: The 'Total RP2D' represents the overall Cohort C considered in this submission. This consists of a combination of patients from 'Phase 1 RP2D' and 'Phase 2 Cohort C' groups.
Abbreviations: CS: company submission; KM: Kaplan Meier; Q2W: biweekly; RP2D: recommended phase II dose.
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO).[5]

Figure 12. OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice (equivalent of Figure 22 and Figure 28 in CS)

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; CS: company submission; HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; NE: not estimable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

Figure 13. OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice and further excluding the availability of subsequent teclistamab or talquetamab in both treatment arms (equivalent of Figure 23 in CS)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; CS: company submission; KM: Kaplan-Meier; NE: not estimable; OS: overall survival.

Figure 14. OS KM curves for talquetamab and ATT-weighted teclistamab (potential future UK clinical practice), i.e. following subsequent treatment adjustment to reflect current UK clinical practice and further inclusion of subsequent teclistamab and talquetamab (equivalent of Figure 24 in CS)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; CS: company submission; KM: Kaplan-Meier; NE: not estimable; OS: overall survival.

Figure 15. TTD KM curves for talquetamab and ATT-weighted teclistamab (corresponds to KM data informing TTD extrapolation for Figure 34 in CS)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; CS: company submission; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

B8. The submission has multiple figures displaying Kaplan-Meier plots for OS. These include Figures 10, 20, 21, 22, 23, 27.

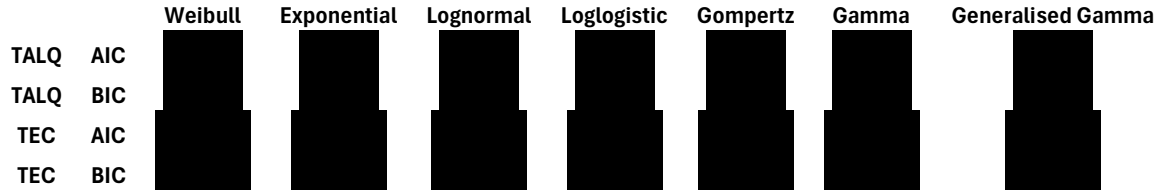
Some of these have numbers at risk at 3-month intervals and some at 5-month intervals. Please supply graphs that currently have risk table at 5-month intervals as versions with risk table at 3-month intervals. As in question B7, for all these Figures please supply the number of events and the number of censorings for each arm.

The requested versions of Figure 10, Figure 21, Figure 22 and Figure 23 from the CS, with 3-month intervals are provided in the response to B7. A summary of which figure represents each figure from the CS is outlined below:

- Figure 11 is the equivalent of Figure 10 from the CS
- Figure 12 is the equivalent of Figure 22 from the CS
- Figure 13 is the equivalent of Figure 23 from the CS
- Figure 14 is the equivalent of Figure 24 from the CS

Please note that Figure 28 from the CS uses the KM data presented in Figure 22 and given this has been supplied as part of Figure 12 of this response, has not been provided again.

B9. The economic model provides AIC and BIC values for parametric models fit to OS survival of talquetamab and teclistamab as below:



<u>PRIORITY QUESTION</u>: Please confirm that these relate to Kaplan-Meier analyses. Please identify the Figure or Figures in the submission that these information criteria refer to.

J&J IM can confirm that these AIC and BIC values relate to the Kaplan-Meier analyses and refer to Figure 34 of Section 3.3.5 in the CS for talquetamab. This figure has been included again below in Figure 16 for reference. The Kaplan-Meier data that was extrapolated is shown in Figure 21 of Section 2.10.5, which has also been provided below in Figure 17 for reference.

Figure 16. Long-term extrapolation of OS for talquetamab using IPD from MonumenTAL-1 (base case following subsequent treatment adjustment)

Abbreviations: IPD: individual patient data; OS: overall survival.

Figure 17. OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; NE: not estimable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

B10. Clinical opinion has been used in several elements of the modelling procedure for OS and PFS pertinent to cost-effectiveness analyses. EAG could find no information about how clinical advisors were "selected" or how many were asked for advice and no information regarding any procedures employed in eliciting clinical advice. Please can the company supply information on these matters.

J&J IM would like to clarify that unless otherwise stated in the CS, clinical expert insights were collected at an advisory board held for the purposes of the talquetamab NICE submission. A report summarising this advisory board report has been supplied as a Data on File accompanying this response. The requested information on the selection of the clinical advisors and advisory board discussion can be found within this report.

J&J IM would like to further note that in the CS (Section 3.5.4, Page 169), reference is made to clinical expert feedback received in TA1015 which indicated that the treatment distribution split for Pomalidomide with Dexamethasone (PomDex)/ Panobinostat with bortezomib and dexamethasone (PanBorDex)/ Selinexor with dexamethasone (SelDex) to be 70%/20%/10%, in 4L+ TCE RRMM in the UK.[23] This was based on percentages agreed upon by clinical experts based on verbal discussions at the recent teclistamab appraisal committee meeting (ACM) (TA1015). In addition to this, as detailed in Appendix A, clinical expert insights collected during the development and appraisal of TA1015 were used to inform the teclistamab curve extrapolations in the ingoing submission. This provided extrapolations for teclistamab for inclusion in the economic model of the ingoing submission, in line with its recently accepted base case extrapolations in TA1015.[23]

Health-state utility values

B11. PRIORITY QUESTION: **In Table 1 of the company submission, it was stated that *"The write-up of the patient-reported outcomes (PRO) data from the pivotal trial informing the clinical effectiveness data for talquetamab (i.e., MonumenTAL-1) was not available in time for the submission deadline and therefore will not be presented. This data will be provided as an addendum when possible."* Please can the company provide further details as to when we can expect to receive this information?**

A summary of the PRO data from MonumenTAL-1 has been provided as an addendum with this response.

B12. Please can the company clarify what assumptions were made in terms of utility values for people that are on-treatment and off-treatment?

J&J IM would like to clarify that the same utility values were used for patients in the same health state who were on-treatment and off-treatment, in line with the approach accepted by NICE for teclistamab in TA1015.[23]

As outlined in Section 3.4.5 of the CS, equal utilities were assumed between talquetamab and teclistamab. Given the majority of patients would only be expected to discontinue treatment upon disease progression (as talquetamab and teclistamab are both treat-to-progression drugs), the simplifying assumption for on- and off-treatment was considered appropriate and associated with minimal uncertainty.

B13. Please can the company clarify whether the utility analysis is based on EQ-5D information collected from the 154 participants in Cohort C or the total MonumenTAL-1 trial population?

J&J IM can confirm that the utility analysis is based on EQ-5D information collected from patients only in Cohort C (N=154), and not the total MonumenTAL-1 trial population.

B14. PRIORITY QUESTION: In Table 59 of the company submission, it is mentioned that the health state utility values are based on the CS model with the lowest AIC. Please can the company provide further details on the statistical models and methods used to derive the base-case PFS and PD utility values from the mapped EQ-5D-3L values?

Progression-free utility

The cost-effectiveness model uses state-dependent mean utility values estimated using mixed models for repeated measures (MMRMs).

Cycle-specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a cycle do not influence the utility estimate for that cycle. This method is aligned with the cost-effectiveness model, where the composition of the cohort in progression-free health state varies over time.

First, for each PRO 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 mapped EQ-5D-3L results up to and including that time point, and using visit (the time at which the EQ-5D-5L data were collected) as a categorical predictor, to get time-specific utility estimates. Details on the mapping of EQ-5D-5L onto the 3L UK value set can be found in Section 3.4.2 of the CS.

The formula used in the MMRMs to estimate the time-specific mean progression-free utility value is as follows:

$$Y = X\beta + \epsilon$$

Where Y is the 1 by N vector that combines all visit results from all subjects included in that MMRM, so that there are $N = \sum_i^n m_i$ observations in total, where m_i is the number of visits for patient i and n is the number of patients. X is the N by p design matrix: each row of X relates to a patient-visit (y_i) observation and has a 1 for visit i and 0 for other visits, and where p is the number of visits included in that MMRM. β is the 1 by p vector of coefficients for visits, estimated in the MMRM. $\in$ is the 1 by N error matrix that has a mean of 0 and variance Ω, which is an N by N matrix that contains subject specific variance-covariance matrices (Σ_i) in its diagonal entries and has 0 values elsewhere. Each subject specific variance-covariance matrix Σ_i is an m by m

matrix that includes the covariance (estimated in the MMRM) between utility values across the visits (the size of each Σ_i depends on how many visits each patient has).

Second, from each of these MMRMs, the marginal (model-based) mean estimate of the last time point was used as the utility estimate for patients still progression free at that time point. These time-specific estimates (each of which was obtained from a different MMRM) are plotted in Figure 18 and their latest time point mean estimates are provided in Table 5. Each of the MMRMs had a compound symmetry (CS) correlation structure, which assumes that variances are homogenous and correlation between time points is constant regardless of their distance. This structure was selected as it had the lowest Akaike Information Criterion (AIC) score among correlation structures in an MMRM and included all mapped EQ-5D-3L measurements in the progression-free state (as presented in Table 6).

The area under the curve of the progression-free estimates was calculated by first linearly interpolating mean values for cycles with a PRO to cycles without a PRO, summing all time-specific means and dividing the sum by the number of cycles. The resulting mean state utility in progression-free state for Cohort C was [redacted] (standard error: [redacted]).

Figure 18. Mean utility estimates (while progression-free and at risk of progression) over time; Cohort C

Abbreviations: EQ5DUTIL: EuroQol five dimensions utility; LS: least squares.

Table 5. Modelled mean utility estimates over time in the progression-free state

Time – 28-day cycles	N at risk	Estimate	SE
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]

Time – 28-day cycles	N at risk	Estimate	SE
9	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]

Abbreviations: SE: standard error.

Post-progression utility

Post-progression health state utilities were estimated from patients with progressed disease in MonumenTAL-1 data (Cohort C).

In the cost-effectiveness model, the progressed-disease health state includes patients who have entered the state at different time points and have been in the state for different amounts of time. The PD state utility was therefore estimated without a time component. All PROs administered after progression were used in an MMRM that does not include visits as covariates and considers correlation between observations from same patients via a correlation matrix. Table 6 shows the AIC estimate from different correlation structures. The mean estimate from the CS model (the lowest AIC) was used in the health economic model for PD health state utility value (mean: [redacted], SE: [redacted]).

Table 6. AIC values of correlation structure in MMRM; Cohort C

Disease state	Compound symmetry structure	AIC	Rank
Progression-free	Autoregression (1)[a]	[redacted]	[redacted]
	Compound symmetry[b]	[redacted]	[redacted]
	Variance components[c]	[redacted]	[redacted]
Progressed disease	Autoregression (1)[a]	[redacted]	[redacted]
	Compound symmetry[b]	[redacted]	[redacted]
	Variance components[c]	[redacted]	[redacted]

Footnotes: [a] Homogenous correlations that decline exponentially with each time step. [b] Homogenous correlation between measurements over time. [c] Zero correlation between measurements over time.
Abbreviations: AIC: Akaike Information Criterion; MMRM: Mixed models for repeated measures.

B15. PRIORITY QUESTION: Please can the company provide their source(s) for the [redacted] utility decrement associated with neurotoxicity presented in Table 58, page 158 of the company submission?

Neurotoxicity is a serious AE that may be associated with severe reductions in health-related quality of life (HRQoL). It was therefore assumed that patients experiencing ≥Grade 3 neurotoxicity have 0 quality of life for the duration of the event, as a conservative assumption. For this reason, a utility decrement of [redacted] (equal to the progression-free utility value) was used to set patient's utility to 0 when they experience ≥Grade 3 neurotoxicity. A similar assumption was also accepted during the appraisal of teclistamab in TA1015, whereby it was assumed that patients experiencing ≥Grade 3 cytokine release syndrome (CRS) had 0 quality of life.[23] Both ≥Grade 3 CRS and neurotoxicity are very serious and require patients to be admitted to intensive care units, which has a further negative impact on their psychological health.[26, 27]

B16. Table 58 states that the utility decrement for infections was obtained from TA559. We have reviewed the committee papers and slides from TA559 but were unable to find this value. Could the company please direct us to the specific table or page where this value can be found?

J&J IM apologise for this typographical error. The utility value for infections (-0.19) was derived from the value for upper respiratory infection (all grades) from TA510 (2018) for daratumumab monotherapy (Table 59; Page 200).[28] This is found in Table 39 (page 161) of the CS for talquetamab.[28]

Resource use and costs

B17. PRIORITY QUESTION: The company stated the proportion of participants who received IVIg following treatment with talquetamab ([redacted] and teclistamab ([redacted] Please can the company confirm whether these proportions were adjusted to reflect subsequent treatment used in a UK clinical practice. Please can the company state what proportion of participants who received teclistamab as a subsequent treatment following talquetamab required IVIg treatment?

J&J IM can confirm that the proportion of patients receiving IVIg with talquetamab and teclistamab were not adjusted to reflect subsequent therapies used in UK clinical practice.

As IVIg use was not explicitly collected for patients receiving IVIg as part of subsequent therapies in MonumenTAL-1, J&J IM are unable to provide the requested information on the proportion of participants who received teclistamab as a subsequent treatment following talquetamab who required IVIg treatment.

However, in order to support the EAG with the exploration of plausible assumptions around the proportion of patients on subsequent teclistamab receiving IVIg treatment in the absence of trial data, J&J IM have provided three additional scenario analyses to account for the costs associated with IVIg use with subsequent teclistamab following talquetamab treatment based on the assumptions outlined below. The results of the additional scenario analyses are presented in Appendix B, alongside the base case economic results.

In the additional scenario analyses, the proportion of patients receiving IVIg with subsequent teclistamab was consistent with those receiving IVIg with initial teclistamab treatment in the model (i.e., [redacted]%). This value is in line with the Committee preferred assumption in TA1015 and validated by clinical expert opinion received by J&J IM as part of this response as broadly appropriate. [23] Patients receiving subsequent teclistamab were modelled to receive two thirds the number of IVIg doses (i.e. 6 doses) compared to patients receiving teclistamab as an initial treatment for TCE RRM, who are modelled to receive 9 doses. This was validated as an appropriate assumption by clinical experts consulted by J&J IM as part of this response, who indicated that patients would receive fewer doses of IVIg when receiving teclistamab as a subsequent treatment following talquetamab, compared to patients who receive teclistamab as an initial treatment for TCE RRMM because time on treatment is likely to decrease following each disease relapse, particularly as patients approach the end of the treatment pathway.

In addition to this, scenario analyses were performed using an upper bound of 9 doses, and lower bound of 3 doses, to account for any uncertainty in this estimate. These additional IVIg costs were implemented in the model as one-off costs in the first cycle of the subsequent treatment calculations using the drug acquisition and administration costs detailed in the CS (Section 3.5.3).

Any use of subsequent IVIg would be dependent on the duration of subsequent bispecific treatment. The duration of subsequent treatments (and thus IVIg use) decreases with each relapse. Therefore, the model links both the percentage of patients receiving subsequent IVIg and the duration of its use proportionally to the IVIg use with initial bispecific treatment.

B18. CS document, Table 70, page 168 states that some participants received lenalidomide + dexamethasone and some received selinexor + dexamethasone but in table 26 (page 99), this has been reported as lenalidomide monotherapy and selixenor monotherapy. Please can the company clarify which is correct?

J&J IM would like to clarify that the reason for this discrepancy is that the MonumenTAL-1 and MajesTEC-1 trials did not explicitly record whether patients received dexamethasone in combination with selinexor or lenalidomide. Consequently, for the purposes of the economic model and as detailed in Table 70 of the CS (Section 3.5.4), a simplifying assumption was made that that patients would receive selinexor and lenalidomide in combination with dexamethasone, which best reflects their use in UK clinical practice. Table 26 of the CS (Section 2.10.4) meanwhile, details the subsequent treatments received by patients as recorded in the MonumenTAL-1 and MajesTEC-1 trials and not how they were ultimately incorporated in the economic model to account for UK clinical practice.

B19. PRIORITY QUESTION: Please clarify the collection of post hoc data for teclistamab IVIg use and explain why the economic model uses a post-hoc analysis. Are other analyses of this outcome available/in existence?

Data on the use of IVIg in patients receiving teclistamab was not a prespecified outcome of the MajesTEC-1 trial, which was the first trial assessing teclistamab specifically in patients with TCE RRMM.[25] The most robust evidence available informing the use of IVIg in patients receiving teclistamab is therefore from the post-hoc analysis from MajesTEC-1. This post-hoc analysis ultimately informed the estimates of IVIg use for teclistamab that were accepted by NICE as part of TA1015.[23]

Adverse events

B20. PRIORITY QUESTION: Please can the company explain the discrepancy between the percentage of people experiencing hypokalemia which reported in Table 41 as [redacted] but in Table 57 as [redacted] Additionally, in Table 57, the proportion of people experiencing pneumonia is [redacted] for talquetamab and [redacted] for teclistamab. However, no such data can be found in the clinical section of the report. In Table 57 the percentage of people experiencing neurotoxicity is [redacted] whereas in Table 43 of the clinical section it is reported as [redacted]

J&J IM apologises for the discrepancy; the correct value for hypokalaemia incidence with teclistamab in MajesTEC-1 is [redacted]% as per Table 41 in the CS. Please note that updated versions of the Company Submission documents (Evidence Submission, Appendices, Cost-Effectiveness Model and Budget Impact Analysis document) have been provided alongside the CQ response to reflect this change.

Pneumonia was not reported in Section 2.11 as part of Table 41 because Table 41 reports the most common Grade 3 or 4 TEAEs that occurred in greater than ≥5% of patients in MonumenTAL-1. As the rate of patients experiencing pneumonia was less than this with talquetamab, it was not included in the table in Section 2.11. The value of [redacted]% for talquetamab can be found in Table TSFAE31RP2DCOHORTC of the MonumenTAL-1 CSR, while the value of [redacted]% for teclistamab can be found in Table 20 of the MajesTEC-1 CSR, both of which are included in the reference pack accompanying this response.

The difference in the reporting of neurotoxicity in Table 57 and Table 43 of the CS is due to the difference in the type of neurotoxicity events reported in both tables. Table 43 presents the incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), which is a subtype of neurotoxicity, rather than all forms of neurotoxicity, which is presented in Table 57, where [redacted] has been correctly reported. It should also be noted that data on ICANS incidence was only collected during the Phase II portion of MonumenTAL-1 (N=118). As such the percentages in Table 43 use N=118 as a denominator, not N=154. J&J IM acknowledges this discrepancy, and corrected this in Table 43 of the updated Evidence Submission.

Technical/model

B21. PRIORITY QUESTION: Please can the company include functionality in the model which allows a scenario that excludes benefit (and costs) associated with subsequent treatment.

As outlined above in the Company response to A15, J&J IM considers that such a scenario which excludes subsequent treatment would not be representative of UK clinical practice wherein majority of patients are expected to receive subsequent treatment. Moreover, removing patients who receive subsequent treatment would result in OS results being heavily dependent on the patients unfit to receive subsequent therapy and thus with the poorest prognosis. This, as well as

the reduced sample size, introduces a substantial level of uncertainty and selection bias for reasons. Therefore, a scenario excluding the benefits associated with subsequent therapies cannot be relied upon for decision-making purposes.

Whilst the costs associated with subsequent treatment could theoretically be removed, this would not be reflective of UK clinical practice. Removing these costs would favour talquetamab in the cost-effectiveness model but would not be representative for decision making given the OS results cannot be adjusted to remove the effects of subsequent treatment as noted above.

As such, J&J IM has not included the functionality in the model allowing for such a scenario which excludes the benefits and costs associated with subsequent treatment.

B22. On page 165, its states that *'The total cost across all events included in the model was* [redacted] *for talquetamab and* [redacted] *for teclistamab, respectively.'* However, setting the costs associated with IVIg to '£0' results in total AE-related costs of [redacted] and [redacted], for treating AEs associated with talquetamab and teclistamab, respectively (obtained from the 'Deterministic Results' worksheet). Please can the company clarify where the additional costs are being incurred.

J&J IM acknowledges this discrepancy and, the values of [redacted] for talquetamab and [redacted] for teclistamab are typographical errors. The values of [redacted] and [redacted] were indeed correct. However, as noted by the EAG in B20, the percentage of patients receiving teclistamab experiencing hypokalaemia should be [redacted]% and not [redacted]%. Following this correction, the new correct values would be £[redacted] and £[redacted], for talquetamab and teclistamab respectively. Note that this does not include costs associated with IVIg.

The total costs of AEs including costs associated with IVIg have been presented in Appendix H2 as part of the disaggregated costs. These costs have been updated accordingly in the updated version of the Appendices provided alongside these CQ responses.

B23. Please can the company confirm if discounting of costs and benefits had been implemented in the model within the first year?

J&J IM can confirm that discount of costs and benefits was implemented within the first year of the economic model. These were applied using one-week model cycles starting from week 2 (cycle 2) of the economic model.

Section C: Textual clarification and additional points

C1. The EAG has been notified that the company are aware that 3 references are missing from the reference pack and will submit these as soon as possible. However, there appear to be more than three “data on file” references missing.

Please ensure that all the following documents are provided (reference numbers and details are from the CS Document B reference list)

15. Johnson & Johnson Innovative Medicine. Data on File. RealiTAL study. 2025

16. Johnson & Johnson Innovative Medicine. Data on File. Market Research report. February 2025.

98. Johnson and Johnson Innovative Medicine. Data on File. MM Caregiver Study Targeted Literature Review Report. 2023.

140. Johnson and Johnson Innovative Medicine. Data on File. MajesTEC-1 Clinical Study Report (September 2021 DCO).

148. Johnson & Johnson Innovative Medicine. Data on File. MonumenTAL-1 Clinical Study Report (May 2022 DCO). 2022. *[the CSR for Sept 2022 DCO is available (ref. 151) – is May 2022 a typo or should this also have been provided?]*

160. Johnson & Johnson Innovative Medicine. Data on File. Subsequent therapies in MonumenTAL-1 (January 2024 DCO).

162. Johnson & Johnson Innovative Medicine. Data on File. 2024. Talquetamab and teclistamab subsequent treatment distributions.

222. Johnson & Johnson Innovative Medicine. Data on File. Post-hoc analysis of IV and SC use for teclistamab.

The following references have been provided in the reference pack alongside the CQ responses:

- Reference 15: Johnson & Johnson Innovative Medicine. Data on File. RealiTAL study. 2025.
- Reference 16: Johnson & Johnson Innovative Medicine. Data on File. Market Research report. February 2025.

- Reference 98: Johnson and Johnson Innovative Medicine. Data on File. MM Caregiver Study Targeted Literature Review Report. 2023.
- Reference 140: Johnson and Johnson Innovative Medicine. Data on File. MajesTEC-1 Clinical Study Report (September 2021 DCO).
- Reference 148: Johnson & Johnson Innovative Medicine. Data on File. MonumenTAL-1 Clinical Study Report (May 2022 DCO). 2022.
- Reference 162: Johnson & Johnson Innovative Medicine. Data on File. 2024. Talquetamab and teclistamab subsequent treatment distributions.
- Reference 222: Johnson & Johnson Innovative Medicine. Data on File. Post-hoc analysis of IV and SC use for teclistamab.

Please note that reference 160 is a duplicate of reference 162.

C2. Appendix B.1.3 states "*A total of 6,588 citations were retrieved from the database searches conducted on 26th May 2020, 22nd January 2021, 27th April 2022, May 2022, February 2023 and October 2023*." However, the total numbers of results from searches recorded in tables 1-7 do not amount to 6,588.

Please explain this discrepancy and confirm whether the June 2021 update should also have been listed here

J&J IM has been in contact with the independent SLR reviewing teams to validate and confirm search results. Given the extensive number of updates and reviewer teams involved, J&J IM is currently in the process of clarifying the EAG's query and expects to be in a position to provide a response to C2 next week.

J&J IM would like to thank the EAG for their understanding on this matter as we seek further clarification on this issue.

C3. Appendix B.1.3 states: "*A total of 1,907 records […] were labelled as "uncertain" and therefore excluded from further analysis.*" A note below the PRISMA diagram, Figure 1, states "*these numbers include compassionate use/expanded access protocols; a decision to include these has been made based on inclusion criteria, but these records may need to be revisited*". Please further describe what is meant by "uncertain", and explain whether these records were "revisited" and the reasons for excluding them from further analysis

J&J IM would like to clarify that the reference to "uncertain" records in the above-mentioned note in the PRISMA diagram relates to specific instances where citation formats, including conference abstracts or clinical trial registries, amongst other records, provided insufficient information at full-text review stage to determine eligibility for inclusion in the final review. For example, some citations noted that "participants received at least three prior therapies" but did not provide further

details about treatment history. In these instances, given the lack of information, the decision to label the citations as “uncertain” was made on a case-by-case basis and discussed between SLR assessors. These citations were excluded at the full-text stage as per indicated in the PRISMA diagram.

In addition, the above-mentioned note in the PRISMA diagram relates to grey literature searches, including records from clinical trial registries and other sources, in which records provided insufficient information to determine eligibility. The information of some of these records, for example records in clinical trial registries, can be updated by trialists on an ongoing basis and therefore is subject to ongoing review, where applicable.

C4. Appendix B.1.3 Table 16 (“*Publications excluded at full-text review stage in original SLR and updates to October 2023*”) lists 1,183 publications, whereas the text in B.1.3 and the PRISMA diagram Figure 1 indicate that 2,013 publications from the database searches were excluded at the full text review stage. Please provide a complete list of excluded publications.

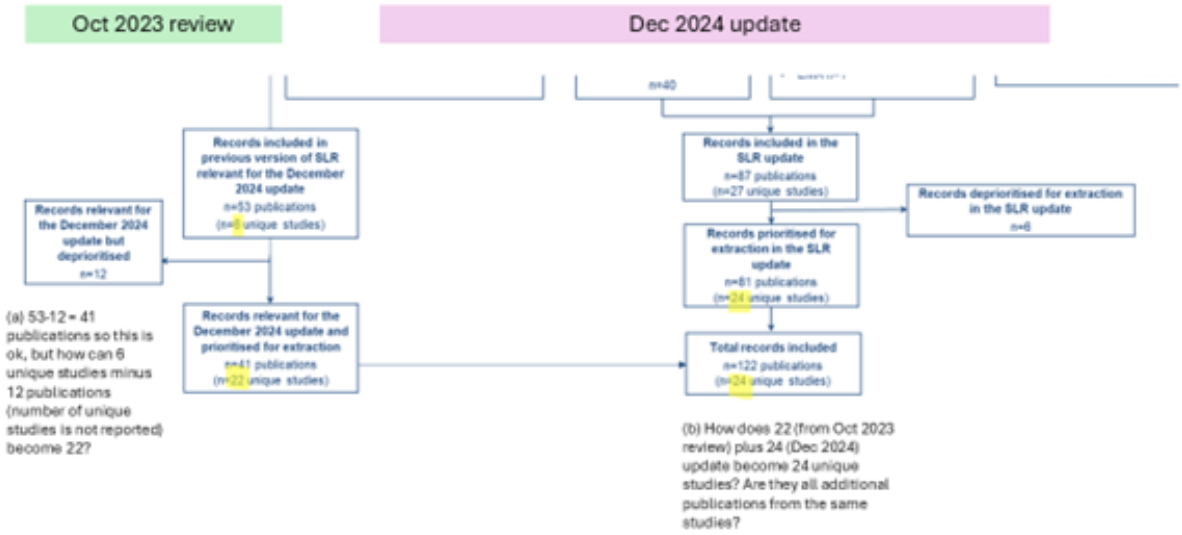
J&J IM can confirm that the difference between the number listed in Table 16 of the CS and the text in B.1.3 and the PRISMA diagram (Figure 1) corresponds to 830 records identified during database search labelled as “uncertain” during the full-text review stage. As outlined in the response to C3, some citation formats provided insufficient information at the full-text review stage to determine eligibility for inclusion in the final review and thus excluded.

As requested, the complete list of excluded publications including the 830 records labelled as “uncertain” has been provided in the Excel file embedded below.

SLR_Records_Full%20Text%20Exclusion.xls

C5. Please correct the numbers of unique studies included in the December 2024 SLR update towards the end of the PRISMA diagram Figure 2 (Appendix B.1.3). Six unique studies from “*records included in previous version of SLR relevant for the December 2024 update*” become 22 unique studies after some are deprioritised, and when these 22 are added to the 24 unique studies from the December 2024 update

the final total is still 24 unique studies. Please see annotations and highlights on the image below (extract from Figure 2) for further illustration.



J&J IM would like to clarify that the value of '22' for unique studies was an error, and should be '4'.

The six unique studies previously identified in the prior SLRs were:

1. MajesTEC-1 Part 1/2 (Phase 1)
2. MajesTEC-1 Part 3 (Phase 2)
3. MonumenTAL-1 Part 1/2 (Phase 1)
4. MonumenTAL-1 Part 3 (Phase 2)

   The different phases of the MajesTEC-1 and MonumenTAL-1 studies were treated as separate, unique studies in line with the previous SLRs.

5. STORM
6. OCEAN

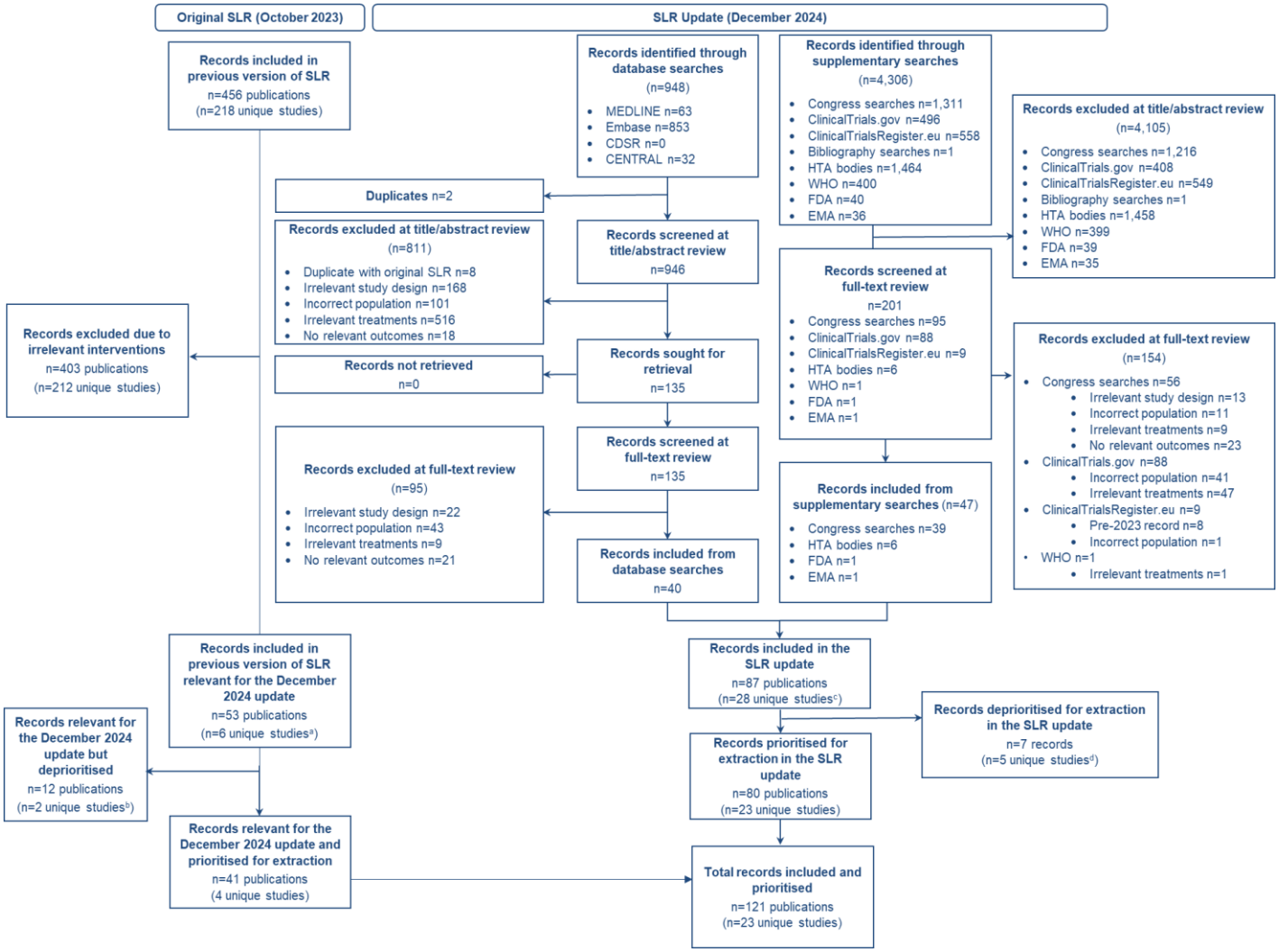
Twelve publications reporting on STORM and OCEAN were then deprioritised for extraction, as they did not report clinical data for patients treated with talquetamab or teclistamab. The final number of unique studies previously captured in the original SLRs that were still relevant for prioritisation has therefore been corrected from 22 to 4.

The total number of unique studies that included as part of the SLR update (not necessarily **novel** studies identified in the update) has also been corrected to 28. Similarly, the total number of unique studies that were extracted as part of the SLR update (not necessarily **novel** studies identified in the update) has also been corrected to 23. The Popat 2024b publication (CS94) reported on both the MajesTEC-1 cohort and an RWE arm of patients treated with pomalidomide plus dexamethasone in England, which would be considered a unique study arm. However,

studies reporting on this intervention were deprioritised, and this publication was erroneously included as a secondary publication to MajesTEC-1 in the included studies table. The below tables have been adjusted to reflect that Popat 2024b is included in the SLR as a unique study, reporting real-world efficacy data for pomalidomide plus dexamethasone (the total number of included/prioritised publications remains unchanged).

The updated PRISMA diagram is provided below in Figure 19:

Figure 19. Updated PRISMA for the clinical SLR update



Footnotes: [a]MajesTEC-1 Part 1/2 (Phase 1), MajesTEC-1 Part 3 (Phase 2), MonumenTAL-1 Part 1/2 (Phase 1), MonumenTAL-1 Part 3 (Phase 2), STORM OCEAN; [b]STORM, OCEAN; [c]The number of unique studies, not the number of novel studies; [d] OCEAN, STORM, Popat 2024a, Popat 2024b, Zhou 2024.

C6. From the 27 unique studies identified in the December 2024 clinical SLR update and listed in Appendix B.1.3, Table 17, please indicate which 24 unique studies were finally included and which 3 unique studies were deprioritised.

As J&J IM have clarified in the answer to C5, the total number of unique studies included in the SLR update has been corrected to 28, and the number of unique studies that were prioritised for extraction to 23. Following on from the answer provided to C5 above, the 23 unique studies that were finally included and extracted are listed in Table 7. The updated table of the five unique studies deprioritised for extraction (with Popat 2024b added), is provided in Table 8.

Table 7. Records included and prioritised for extraction – December 2024 SLR update

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
Appelman 2024	1	NA	Appelman M, Oostvogels R, Geerts PA, et al. Bispecific Antibodies for Multiple Myeloma in the Real World: Lessons Learnt from a Nation-Wide Dutch Observational Registry. Blood 2024;144:7008. (ID CS147)	Congress searches
Costa 2024	2	NA	Costa B, Tan C, Shekarkhand T, et al. P-012 Real-World Safety and Early Efficacy of Talquetamab in Patients with Heavily-Pretreated Relapsed/Refractory Multiple Myeloma. Clinical Lymphoma Myeloma and Leukemia 2024;24:S46-S47. (ID CS199)	Congress searches
Dhakal 2024	3	NA	Dhakal B, Kim N, John W, et al. Real-World Patient Characteristics and Outcomes in Patients with High-Risk Cytogenetic Relapsed or Refractory Multiple Myeloma Receiving Teclistamab across Community Oncology Practices in the US. Blood 2024;144:7854. (ID CS143)	Congress searches
Dima 2024	4	NA	Dima D, Davis JA, Ahmed N, et al. Real-World Safety and Efficacy of Teclistamab for Patients with Heavily Pretreated Relapsed-Refractory Multiple Myeloma. Blood 2023;142(Supplement 1):91. (ID 368)	Database searches
			Dima D, Sannareddy A, Ahmed N, et al. Toxicity and Efficacy Outcomes of Teclistamab in Patients with Relapsed-Refractory Multiple Myeloma (RRMM) Above the Age of 70 Years: A Multicenter Study. Blood 2023;142(Supplement 1):3330. (ID 466)	Database searches
			Dima D, Davis J, Ahmed N, et al. Safety and Efficacy of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma: A Real-World Experience from the US Myeloma Innovations Research Collaborative (USMIRC). Transplantation and Cellular Therapy 2024;30(2 Supplement):S384. (ID 319)	Database searches
			Dima D, Davis JA, Ahmed N, et al. Safety and Efficacy of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma: A Real-World Experience. Transplantation and	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Cellular Therapy 2024;30(3):308.e1-308.e13. (ID 274)	
Faiman 2023	5	NA	Faiman B, Dima D, Duco M, et al. P-256 Initial report of a single institution experience with teclistamab for relapsed or refractory multiple myeloma including prior BCMA. Clinical Lymphoma Myeloma and Leukemia 2023;23:S177. (ID CS190)	Congress searches
Firestone 2023	6	NA	Firestone R, Shekarkhand T, Patel D, et al. Evaluating the efficacy of commercial teclistamab in relapsed refractory multiple myeloma patients with prior exposure to anti-BCMA therapies. Journal of Clinical Oncology 2023;41(16 Supplement):8049. (ID 633)	Database searches
Ghamsari 2024	7		Ghamsari F, Trando A, Medley K, et al. Real-world outcomes of teclistamab for the treatment of relapsed/refractory multiple myeloma at UC San Diego Health: A single-institution experience. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2024;42. (ID 171)	Database searches
Gordon 2023	8	NA	Gordon B, Fogel L, Varma G, et al. Teclistamab Demonstrates Clinical Activity in Real-World Patients Ineligible for the Pivotal Majestec-1 Trial. Blood 2023;142(Supplement 1):4741. (ID 492)	Database searches
Ishida 2024	9	NA	Ishida T, Kuroda Y, Matsue K, et al. A Phase 1/2 study of teclistamab, a humanized BCMA x CD3 bispecific Ab in Japanese patients with relapsed/refractory MM. International Journal of Hematology. 2024. (ID 39)	Database searches
			Shinsuke Iida YK, Kosei Matsue, Takuya Komeno, Takuro Ishiguro, Jun Ishikawa, Toshiro Ito, Hiroshi, Kosugi KS, Kazuko Nishikawa, Kazuhiro Shibayama, Hiroshi Yamazaki, Mitsuo Inagaki, Hisanori, Kobayashi TI. Primary Results Of A Phase 1/2 Study Of Teclistamab, A B-Cell Maturation Antigen (Bcma) X Cd3 Bispecific Antibody, In Japanese Patients With Relapsed/Refractory Multiple Myeloma (Rrmm): American Society of Clinical Oncology, 2024. (ID CS93)	Database searches
MajesTEC-1 (Part 1-3, Phase 1/2)a	10, 11	NCT03145181 / NCT04557098	Martin TG, Mateos MV, Nooka A, et al. Detailed overview of incidence and management of cytokine release syndrome observed with teclistamab in the MajesTEC-1 study of patients with relapsed/refractory multiple myeloma. Cancer 2023;129(13):2035-2046. (ID 784)	Database searches
			Usmani SZ, Karlin L, Benboubker L, et al. Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study. Journal of Clinical	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Oncology 2023;41(16 Supplement):8034. (ID 599)	
			Usmani SZ, Karlin L, Benboubker L, et al. Durability of Responses With Biweekly Dosing of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma Achieving a Clinical Response in the MajesTEC-1 Study. Clinical Lymphoma, Myeloma and Leukemia 2023;23(Supplement 1):S477. (ID 720)	Database searches
			Van De Donk NWCJ, Garfall AL, Benboubker L, et al. Evaluation of prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) to inform the management of patients (pts) treated with teclistamab in MajesTEC-1. Journal of Clinical Oncology 2023;41(16 Supplement):8033. (ID 600)	Database searches
			Van De Donk NWCJ, Bahlis N, Costa LJ, et al. Impact of Covid-19 on Outcomes with Teclistamab in the Phase 1/2 Majestec-1 Study in Patients with Relapsed/Refractory Multiple Myeloma. Haematologica 2024;109(Supplement 2):31. (ID 220)	Database searches
			Van De Donk NWCJ, Garfall AL, Benboubker L, et al. Longer-term follow-up of patients (pts) receiving prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) in the phase 1/2 MajesTEC-1 study of teclistamab in relapsed/refractory multiple myeloma (RRMM). Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2024;42. (ID 183)	Database searches
			van de Donk N, Moreau P, Garfall A, et al. Long-Term Follow-Up From MajesTEC-1 of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Patients With Relapsed/ Refractory Multiple Myeloma (RRMM). Clinical Lymphoma, Myeloma and Leukemia 2023;23(Supplement 1):S477-S478. (ID 711)	Database searches
			Van De Donk NWCJ, Moreau P, Garfall AL, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). Journal of Clinical Oncology 2023;41(16 Supplement):8011. (ID 616)	Database searches
			Van De Donk NW, Moreau P, Garfall AL, et al. Long-term follow-up from MajesTEC-1 of Teclistamab, a B-cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in patients with Relapsed/Refractory Multiple Myeloma (RRMM). Oncology Research and Treatment 2023;46(Supplement 5):124. (ID 658)	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Costa LJ, Donk N, Rosinol L, et al. Long-Term Follow-up from the Phase 1/2 Majestec-1 Trial of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma: Subgroup Analysis by Lines of Therapies. Hematology, Transfusion and Cell Therapy 2024;46(Supplement 4):S515. (ID 87)	Database searches
			van de Donk NW, Garfall AL, Benboubker L, et al. MM-344 Longer-Term Follow-up of Patients Receiving Prophylactic Tocilizumab for the Reduction of Cytokine Release Syndrome (CRS) in the Phase 1/2 MajesTEC-1 Study of Teclistamab in Relapsed/Refractory Multiple Myeloma (RRMM). Clinical Lymphoma, Myeloma and Leukemia 2024;24(Supplement 1):S549. (ID 693)	Database searches
			Donk N, Popat R, Rosiol L, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma (Rrmm): Majestec-1 Subgroup Analysis by Lines of Therapies. Hematology, Transfusion and Cell Therapy 2023;45(Supplement 4):S397-S398. (ID 108)	HTA searches
			Touzeau C, Krishnan AY, Moreau P, et al. Efficacy and safety of teclistamab in patients with relapsed/refractory multiple myeloma after BCMA-targeting therapies. Blood. 2024. (ID HTA16)	HTA searches
			CDA-AMC. teclistamab. PC0332-000, 2023. (ID HTA3)	HTA searches
			NICE. Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments. TA1015, 2024. (ID HTA 8)	Congress searches
			SMC. teclistamab (Tecvayli). SMC2668, 2024. (ID HTA8)	Congress searches
			Surbhi Sidana PM, Alfred Garfall, Manisha Bhutani, Albert Oriol, Ajay Nooka, Thomas Martin, Laura Rosiñol Dachs, Maria, Victoria Mateos, Nizar J Bahlis, Rakesh Popat, Britta Besemer, Joaquín Martinez-Lopez, Amrita Krishnan, Michel Delforge, Danielle Trancucci, Raluca Verona, Tara Stephenson, Katherine Chastain, Niels W.C.J. Van De Donk. P879 long-term follow-up from majestec-1 of teclistamab, a b-cell maturation antigen(bcma) x cd3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). HemaSphere 2023;7:1654. (ID CS100)	Congress searches
			Manisha Bhutani AG, Katarina Uttervall, Saad Z Usmani, Lionel Karlin, Lotfi Benboubker, Hareth Nahi, Jesús San Miguel, Danielle Trancucci, Keqin Qi, Tara Stephenson, Alfredo Perales-Puchalt, Katherine Chastain, Ajai Chari. P881 durability of responses with	Congress searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			biweekly dosing of teclistamab in patients withrelapsed/refractory multiple myeloma achieving a clinical response in the majestec-1 study. HemaSphere 2023;7:1658. (ID CS101)	
			Matous JV, van de Donk NW, Oriol A, et al. Higher Teclistamab Step-up Dosing in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Results from the Majestec-1 Trial. Blood 2024;144:4749. (ID CS45)	Congress searches
			Usmani S, Bahlis NJ, Costa L, et al. P-089 Impact of COVID-19 on Outcomes With Teclistamab in the Phase 1/2 MajesTEC-1 Study in Patients With Relapsed/Refractory Multiple Myeloma. Clinical Lymphoma Myeloma and Leukemia 2024;24:S93. (ID CS221)	Congress searches
			Rosiñol L, Garfall A, Benboubker L, et al. P-074 Longer-Term Follow-Up of Patients Receiving Prophylactic Tocilizumab for Cytokine Release Syndrome in the Phase 1/2 MajesTEC-1 Study of Teclistamab in Relapsed/Refractory Multiple Myeloma. Clinical Lymphoma Myeloma and Leukemia 2024;24:S84-S85. (ID CS214)	Congress searches
			Moreau P, NWCJVDD, MD, et al. P979 patient-reported outcomes for teclistamab versus real-world physician's choice of therapy in the locommotion study in patients with triple-class exposed relapsed/refractory multiple myeloma. HemaSphere 2023;7:1857. (ID CS111)	Congress searches
			van de Donk NW, Moreau P, Garfall AL, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): American Society of Clinical Oncology, 2023. (ID CS232)	Congress searches
			Popat R, Nooka A, Moreau P, et al. Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma. Clinical Lymphoma Myeloma & Leukemia 2024;24:S80-S80. (ID CS212)	Congress searches
			Garfall AL, Nooka AK, van de Donk NW, et al. Long-term follow-up from the phase 1/2 MajesTEC-1 trial of teclistamab in patients with relapsed/refractory multiple myeloma: American Society of Clinical Oncology, 2024. (ID CS23)	Congress searches
			van de Donk N, Nooka A, Rodriguez C, et al. OA-51 Preliminary recommendations for prevention and management of infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab based on	Congress searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			experience from the MajesTEC-1 study. Clinical Lymphoma Myeloma and Leukemia 2023;23:S32. (ID CS182)	
			Catamero D, Benito PB, Shenoy S, et al. NSP-04 Managing infections, hypogammaglobulinemia, and neutropenia during treatment with teclistamab in relapsed/refractory multiple myeloma: nurse-led experience from the MajesTEC-1 study. Clinical Lymphoma Myeloma and Leukemia 2023;23:S315. (ID CS196)	Congress searches
			Martin TG, Mateos M-V, van de Donk NW, et al. Pooled Efficacy and Safety of Teclistamab in 217 Patients with Triple-Class Exposed Relapsed/Refractory Multiple Myeloma from 3 Registrational Clinical Studies. Blood 2024;144:3331. (ID CS41)	Congress searches
			Luciano J. Costa NJB, Saad Z Usmani, Niels W.C.J. van de Donk, Ajay Nooka, Aurore Perrot, Keqin Qi,, Caroline Hodin CU, Athena Zuppa, Katherine Chastain, Margaret Doyle, Maria-Victoria Mateos. Efficacy and safety of teclistamab in patients with relapsed/refractory multiple myeloma with high-risk features: a subgroup analysis from the phase 1/2 majestec-1 study: American Society of Clinical Oncology, 2024. (ID CS83)	Congress searches
			Katarina Uttervall NWCJvdD, Alfred Garfall, Lotfi Benboubker, Kaz Groen, Laura Rosiñol, Jeffrey Matous,, Deeksha Vishwamitra CH, Tara Stephenson7, Keqin Qi, Athena Zuppa, Katherine Chastain, Maria-Victoria, Mateos. Longer-Term Follow-Up Of Patients Receiving Prophylactic Tocilizumab For Reduction Of Cytokine Release Syndrome In The Phase 1/2 Majestec-1 Study Of Teclistamab In Relapsed/Refractory Multiple Myeloma: American Society of Clinical Oncology, 2024. (ID CS84)	Congress searches
			Albert Oriol RP, Alfred Garfall, Ajay Nooka, Niels W.C.J. van de Donk, Philippe Moreau, Manisha Bhutani,Thomas Martin, Laura Rosiñol, Maria-Victoria Mateos, Nizar J Bahlis, Britta Besemer, Joaquin Martinez Lopez, Amrita Krishnan, Michel Delforge, Lin Huang, Deeksha Vishwamitra, Tara Stephenson, Katherine Chastain, Surbhi Sidana. Long-Term Follow-Up From The Phase 1/2 Majestec-1 Trial Of Teclistamab In Patients With Relapsed/Refractory Multiple Myeloma: American Society of Clinical Oncology, 2024. (ID CS86)	Congress searches
			Zhen Cai Z-JX, Aili He, Yujun Dong, Yafei Wang, Aijun Liao, Yang Song, Juanjuan Song, Clarissa Uhlar, Katherine Chastain, Latisha Watkins, Xinchao Luo, Lin Huang,	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Zhuolu Niu, Natalia A. Quijano Cardé, Yue Guo, Hongmei, Xu RV, Longen Zhou, Jingyun Li, Ting Niu, Weijun Fu, Juan Du. Results From The China Cohort Of The Phase 1/2 MajesTEC-1 Study Of Teclistamab (Tec) Treatment In Patients (Pts) With Triple-Class Exposed Relapsed/Refractory Multiple Myeloma (RRMM): American Society of Clinical Oncology, 2024. (ID CS92)	
Manjrah 2024	12	NA	Manjrah H, Brisou G, Noël R, et al. P-049 Teclistamab in Real Life: Can We Shorten the Ramp-Up? Clinical Lymphoma Myeloma and Leukemia 2024;24:S69. (ID CS206)	Congress searches
Marin 2023	13	NA	Marin E, Scott S, Maples K, et al. Prophylactic Tocilizumab to Prevent Cytokine Release Syndrome (CRS) with Teclistamab Administration. Blood 2023;142(Supplement 1):2008. (ID 489)	Database searches
Mohan 2023	14	NA	Mohan M, Shah N, Luan D, et al. Teclistamab in Relapsed Refractory Multiple Myeloma: Multi-Institutional Real-World Study. Blood 2023;142(Supplement 1):545. (ID 420)	Database searches
MonumenTAL-1 (Part 1/2, Phase 1/2)	15 - 16	NCT03399799 / NCT04634552	Rasche L, Schinke C, Touzeau C, et al. MM-492 Long-term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5DxCD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma (RRMM). Clinical Lymphoma, Myeloma and Leukemia 2024;24(Supplement 1):S561-S562. (ID 134)	Database searches
			Sanchez L, Schinke C, Krishnan A, et al. Clinical Outcomes of Subsequent Therapies in Patients with Relapsed/Refractory Multiple Myeloma Following Talquetamab Treatment: Analyses from the Phase 1/2 MonumenTAL-1 Study. Blood 2023;142(Supplement 1):2007. (ID 348)	Database searches
			Schinke C, Touzeau C, Oriol A, et al. Symptoms, Functioning, and Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Treated with Talquetamab: Updated Patient-Reported Outcomes from the Phase 1/2 MonumenTAL-1 Study. Blood 2023;142(Supplement 1):6711. (ID 392)	Database searches
			Jakubowiak AJ, Anguille S, Karlin L, et al. Updated Results of Talquetamab, a GPRC5DxCD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma with Prior Exposure to T-Cell Redirecting Therapies: Results of the Phase 1/2 MonumenTAL-1 Study. Blood 2023;142(Supplement 1):3377. (ID 405)	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Chari A, Oriol A, Krishnan A, et al. Efficacy and Safety of Less Frequent/Lower Intensity Dosing of Talquetamab in Patients with Relapsed/Refractory Multiple Myeloma: Results from the Phase 1/2 MonumenTAL-1 Study. Blood 2023;142(Supplement 1):1010. (ID 417)	Database searches
			Schinke CD, Touzeau C, Minnema MC, et al. Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DxCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM). Journal of Clinical Oncology 2023;41(16 Supplement):8036. (ID 598)	Database searches
			Schinke C, Touzeau C, Minnema MC, et al. Pivotal Phase 2 MonumenTAL-1 results of Talquetamab (tal), a GPRC5DxCD3 Bispecific Antibody (BsAb), for Relapsed/ Refractory Multiple Myeloma (RRMM). Oncology Research and Treatment 2023;46(Supplement 5):82-83. (ID 653)	Database searches
			Rodriguez-Otero P, Schinke C, Chari A, et al. Analysis of Infections and Parameters of Humoral Immunity in Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM) Treated With Talquetamab (tal) Monotherapy in MonumenTAL-1. Clinical Lymphoma, Myeloma and Leukemia 2023;23(Supplement 1):S480. (ID 706)	Database searches
			Minnema MC, Chari A, Touzeau C, et al. Phase 1/2 Results of Talquetamab, a G Proteincoupled Receptor Family C Group 5 Member D X Cd3 Bispecific Antibody, in Patients with Relapsed/ Refractory Multiple Myeloma (Rrmm) (Monumental-1). HemaSphere 2023;7(Supplement 2):26-27. (ID 758)	Database searches
			Van De Donk N, Rasche L, Touzeau C, et al. Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Treated with Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D X Cd3 Bispecific Antibody, from Monumental-1. HemaSphere 2023;7(Supplement 2):34. (ID 772)	Database searches
			European Medicines Agency. Assessment report. Talvey. Volume 2025, 2024. (ID EMA1)	EMA searches
			FDA. FDA grants accelerated approval to talquetamab-tgvs for relapsed or refractory multiple myeloma, 2023. (ID FDA1)	FDA searches
			CDA-AMC. talquetamab. PC0363-000, 2024. (ID HTA 13)	HTA searches
			Leo Rasche CS, Ajai Chari, Brea C. Lipe, Noa Lavi, Paula Rodríguez-Otero, Deeksha Vishwamitra, Sheri Skerget, Raluca Verona, Xuewen Ma, Sheetal Khedkar, Brandi Hilder,	Congress searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Tara Masterson, Michela Campagna, Thomas Renaud, Jaszianne Tolbert, Christoph Heuck, Damiette, Smit NWCJVDD. P892 analysis of infections and parameters of humoral immunity in patients (pts) with relapsed/refractory multiple myeloma (rrmm) treated with talquetamab (tal) monotherapy in monumental-1. HemaSphere 2023;7:1681. (ID CS102)	
			Krishnan A, Costa L, Schinke C, et al. P-023 Talquetamab, a G protein–coupled receptor family C group 5 member D× CD3 bispecific antibody, in relapsed/refractory multiple myeloma: efficacy and safety of patient subgroups from monumenTAL-1. Clinical Lymphoma Myeloma and Leukemia 2023;23:S45-S46. (ID CS185)	Congress searches
			Purcell K, Catamero D, Dai V, et al. NSO-07 Management considerations for dermatologic toxicities associated with talquetamab, a GPRC5D× CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. Clinical Lymphoma Myeloma and Leukemia 2023;23:S312-S313. (ID CS194)	Congress searches
			Leo Rasche CS, Cyrille Touzeau, Monique Minnema, Niels W.C.J. van de Donk, Paula Rodríguez-Otero, Maria-Victoria Mateos, Jing Christine Ye, Deeksha Vishwamitra, Indrajeet Singh, Xiang Qin, Michel Campagna, Tara Masterson, Brandi Hilder, Jaszianne Tolbert, Thomas Renaud, Christoph Heuck, Colleen Kane, Ajai Chari. Long-term efficacy and safety results from the phase 1/2 monumental-1 study of Talquetamab, a gprc5d×cd3 bispecific antibody, in patients with relapsed/refractory multiple myeloma: American Society of Clinical Oncology, 2024. (ID CS82)	Congress searches
			Schinke C, Morgan G, Costa LJ, et al. Clinical Outcomes in Black Patients with Relapsed/Refractory Multiple Myeloma Following Talquetamab Treatment: Analyses from the Phase 1/2 Monumental-1 Study. Blood 2024;144:3357. (ID CS144)	Congress searches
			Ito S, Kuroda Y, Sunami K, et al. Efficacy and Safety of Talquetamab, a GPRC5D× CD3 Bispecific Antibody, in Japanese Patients with Relapsed/Refractory Multiple Myeloma from the Phase 1/2 Monumental-1 Study. Blood 2024;144:7011. (ID CS146)	Congress searches
			Gang An JJ, Zhen Cai, Hongmei Jing, Chengcheng Fu, Pengcheng He, Zhong-Jun Xia, Rui Liu, Liang Li, Xue, Gai HZ, Dian Zhu, Xinchao Luo, Binbin Sun, Hongmei Xu, Longen Zhou, Michela Campagna, Tara Masterson, Bonnie Lau, Thomas Renaud,	Congress searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Christoph Heuck, Indrajeet Singh, Deeksha Vishwamitra, Lugui Qiu. Efficacy And Safety Of Talquetamab, A Gprc5D×Cd3 Bispecific Antibody, In Chinese Patients With Relapsed/Refractory Multiple Myeloma From The Phase 1/2 Monumental-1 Study: American Society of Clinical Oncology, 2024. (ID CS90)	
			Morillo D, Chamorro CM, Manteca M-VM, et al. P-058 Cytokine Release Syndrome in Patients Receiving Alternative Step-Up Doses of Talquetamab for Relapsed/Refractory Multiple Myeloma: Results from the Phase 1/2 MonumenTAL-1 Study. Clinical Lymphoma Myeloma and Leukemia 2024;24:S74-S75. (ID CS208)	Congress searches
			Schinke C, Vij R, Jagannath S, et al. P-077 Prophylactic Tocilizumab to Mitigate Cytokine Release Syndrome in Patients Receiving Talquetamab for Relapsed/Refractory Multiple Myeloma: Results From the Phase 1/2 MonumenTAL-1 Study. Clinical Lymphoma Myeloma and Leukemia 2024;24:S86. (ID CS215)	Congress searches
			Ye JC, Schinke C, Touzeau C, et al. P-098 Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D× CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma. Clinical Lymphoma Myeloma and Leukemia 2024;24:S99. (ID 223)	Congress searches
			Ma X, Gong J, Zhou J, et al. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) support for talquetamab (tal) QW and Q2W dosing in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Analyses from MonumenTAL-1: American Society of Clinical Oncology, 2023. (ID CS33)	Congress searches
MonumenTAL-1 (Part 3, Phase 2)	16	NCT04634552	Touzeau C, Schinke C, Minnema M, et al. S191: Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DXCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM). Hemasphere 2023;7:e5955094. (ID CS96)	Congress searches
OPTec	17	NCT05972135	Rifkin RM, Schade HH, Simmons G, et al. OPTec: A phase 2 study to evaluate outpatient (OP) step-up administration of teclistamab (Tec), a BCMA-targeting bispecific antibody, in patients (pts) with relapsed/refractory multiple myeloma (RRMM). Journal of Clinical Oncology. Conference: Annual Meeting of the American	Database searches

Study Name Trial Registry Number	#	Trial Identification Number	Reference (RefID)	Source
			Society of Clinical Oncology, ASCO 2024;42. (ID 165)	
Pericole 2024	18	NA	Pericole F, Lima JS, Ottoni E, et al. P-278 Brazilian Relapsed Refractory Multiple Myeloma Patients Treated with Teclistamab Outside of Clinical Trials as an Expanded Access Program. Clinical Lymphoma Myeloma and Leukemia 2024;24:S196-S197. (ID CS227)	Congress searches
Perrot 2024	19	NA	Perrot A, Hulin C, Harel S, et al. P-065 Effectiveness and Safety of Teclistamab in Triple-Class Exposed Relapsed/Refractory Multiple Myeloma: Results of the French Real-World RetrosTECtive Study. Clinical Lymphoma Myeloma and Leukemia 2024;24:S78-S79. (ID CS210)	Congress searches
Stepanovic 2023	20	NA	Stepanovic A, Abonour R, Abu Zaid M, et al. Teclistamab in Relapsed/Refractory Multiple Myeloma: Real-World Outcomes at a Single Academic Center in the Midwest. Blood 2023;142(Supplement 1):7359. (ID 460)	Database searches
Strifler 2023	21	NA	Strifler S, Wendelin K, Hefter C, et al. Promising real-world data of treatment with two BCMAtargeting bispecific T-cell engagers in extensively pretreated myeloma patients. Oncology Research and Treatment 2023;46(Supplement 5):313. (ID 670)	Database searches
Tabbara 2024	22	NA	Tabbara N, Singel M, Allen N, et al. Ambulatory teclistamab administration in patients with relapsed/refractory multiple myeloma. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2024;42. (ID 187)	Database searches
Venkatesh 2023	23	NA	Venkatesh P, Atrash S, Paul B, et al. Efficacy of teclistamab in patients (pts) with heavily pretreated, relapsed/refractory multiple myeloma (RRMM), including those refractory to penta RRMM and BCMA (Bcell maturation antigen) directed therapy (BDT). Journal of Clinical Oncology 2023;41(16 Supplement):e20044. (ID 618)	Database searches

[a].The phase I and phase II components of the MajesTEC-1 and MonumenTAL-1 trials were each classed as unique studies, as they had separate trial registration numbers, however multiple records reported on the entire Phase 1/2 trial. No records reporting specifically on Phase 2 of the MajesTEC-1 trial were included in the clinical SLR update.

Table 8. Records included in the clinical SLR update but deprioritised for extraction

Study Name Trial Registry Number	Trial Identification Number	Reference (RefID)	Source
OCEAN	NCT03151811	Schjesvold FH, Ludwig H, Delimpasi S, et al. EE73 Ocean (OP-103): Patients with Relapsed/Refractory Multiple Myeloma Treated with Melflufen Plus Dexamethasone or Pomalidomide Plus Dexamethasone-a Resource Utilization	Congress searches

		Analysis of Adverse Events Leading to Hospitalizations. Value in Health 2023;26:S64. (ID CS18)	
STORM	NCT02336815	Cole C, Opalikhin AM, McCartney M, et al. Racial differences in outcomes of patients with relapsed/refractory multiple myeloma treated with selinexor. Journal of Clinical Oncology 2023;41(16 Supplement):e20016. (ID 637)	Database searches
		NICE. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments. TA970, 2024. (ID HTA2)	HTA searches
		SMC. selinexor (Nexpovio). SMC2673, 2024. (ID HTA9)	HTA searches
Popat 2024a	NA	Popat R, Greenwood A, Wilson W, et al. P-144 Oral Symptom Assessment Using Patient Reported Outcomes (PRO) for Relapsed Multiple Myeloma Patients Treated with Talquetamab. Clinical Lymphoma Myeloma and Leukemia 2024;24:S123. (ID CS225)	Congress searches
Popat 2024b	NR	Popat R, Jenner M, Ghilotti F, van Nimwegen K, Lied-Lied A, Ming T, Cheah E, Melrose D, Caravotas L, Diels J. Comparative Efficacy of Teclistamab Versus Pomalidomide Plus Dexamethasone for Patients with Triple-Class Exposed Relapsed Refractory Multiple Myeloma in England. *American Society of Clinical Oncology*. 2024. (ID CS94)	Congress searches
Zhou 2024	NA	Zhou H, Wang Y, Chen J, et al. Efficacy and safety of generic pomalidomide plus low-dose dexamethasone in relapsed or refractory multiple myeloma: a multicenter, open-label, single-arm trial. Annals of Hematology 2024;103(3):855-868. (ID 554)	Database searches

C7. Please provide lists of the 403 publications/212 unique studies excluded from the previous version of the clinical SLR (to October 2023) due to irrelevant interventions, and of the 12 records "*relevant for the December 2024 update but deprioritised"* (Appendix B.1.3, Figure 2 PRISMA diagram).

The list of the 212 unique studies from the original SLRs that were not relevant for the current clinical SLR update is provided in the embedded document, below:

List of Studies Excluded from the Ori

The 12 records (reporting on two unique studies, OCEAN and STORM) deprioritised at the extraction stage of the December 2024 update are listed in Table 9, below. These studies were deprioritised as they did not report clinical data for patients treated with talquetamab or teclistamab.

Table 9. Records included from the previous SLR but deprioritised for presentation in the results tables

Study Name	Publication Name and ID	Citation
OCEAN	Dimopoulos 2021 (6520)	Dimopoulos MA, Schjesvold FH, Mateos MV, et al. OCEAN (OP-103): Melflufen Plus Dexamethasone (Dex) Versus Pomalidomide (Pom) and Dex in Relapsed/Refractory Multiple Myeloma (RRMM) - Impact of Prior Treatments Analysis. Blood 2021;138:4780
STORM	Vogl 2016 (860)	Vogl DT, Dingli D, Cornell RF, et al. Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti- CD38 Ab refractory multiple myeloma (MM): STORM study. 2016;128
	Yee 2019 (1046)	Yee AJ, Huff CA, Chari A, et al. Response to therapy and the effectiveness of treatment with selinexor and dexamethasone in patients with penta-exposed triple-class refractory myeloma who had plasmacytomas. Blood 2019;134
	Nooka 2019 (1117)	Nooka AK, Yee AJ, Huff CA, et al. Influence of cytogenetics in patients with relapsed refractory multiple myeloma treated with oral selinexor and dexamethasone: A post-hoc analysis of the storm study. Blood 2019;134.
	Chari 2019 (1166)	Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. New England Journal of Medicine 2019;381:727.
	Vogl 2019 (1342)	Vogl DT, Nooka A, Gavriatopoulou M, et al. Improvements in Renal Function with Selinexor in Relapsed/Refractory Multiple Myeloma: Post-hoc Analyses from the STORM Study. Clinical Lymphoma, Myeloma and Leukemia 2019;19:e118
	Gavriatopoulou 2019 (1391)	Gavriatopoulou M, Vogl DT, Nooka A, et al. Effect of Age on the Safety and Efficacy of Selinexor in Patients with Relapsed Refractory Multiple Myeloma: A Post-hoc Analysis of the STORM Study. Clinical Lymphoma, Myeloma and Leukemia 2019;19:e117.

	Vogl 2018 (1472)	Vogl DT, Dingli D, Cornell RF, et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. Journal of Clinical Oncology 2018;36:859.
	Lonial 2017 (IMW_37)	Lonial S, Vogl DT, Chen C, et al. Oral Selinexor Shows Single Agent Activity Enhanced With PI or IMID Combinations in Refractory Multiple Myeloma (MM). Clinical Lymphoma, Myeloma and Leukemia 2017;17:e13-e14.
	CTG_313	ClinicalTrials.gov. Selinexor treatment of refractory myeloma (STORM).
	T-EMA_1	Agency EM. Assessment report: Nexpovio 2021.
	PBAC 2021 (2022-PBAC_1005)	PBAC. Public Summary Document – July 2021 PBAC Meeting. 5.08 SELINEXOR, Tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd., 2021:29.

C8. Please explain why the exclusion criteria "*prior treatment with CAR-T*" and "*prior treatment targeted to BCMA*" were removed for the October 2023 and December 2024 versions of the clinical SLRs, and whether records excluded prior to October 2023 were re-screened in case any records had been excluded based on these criteria. (See Appendix B.1.2, Tables 13 and 14)

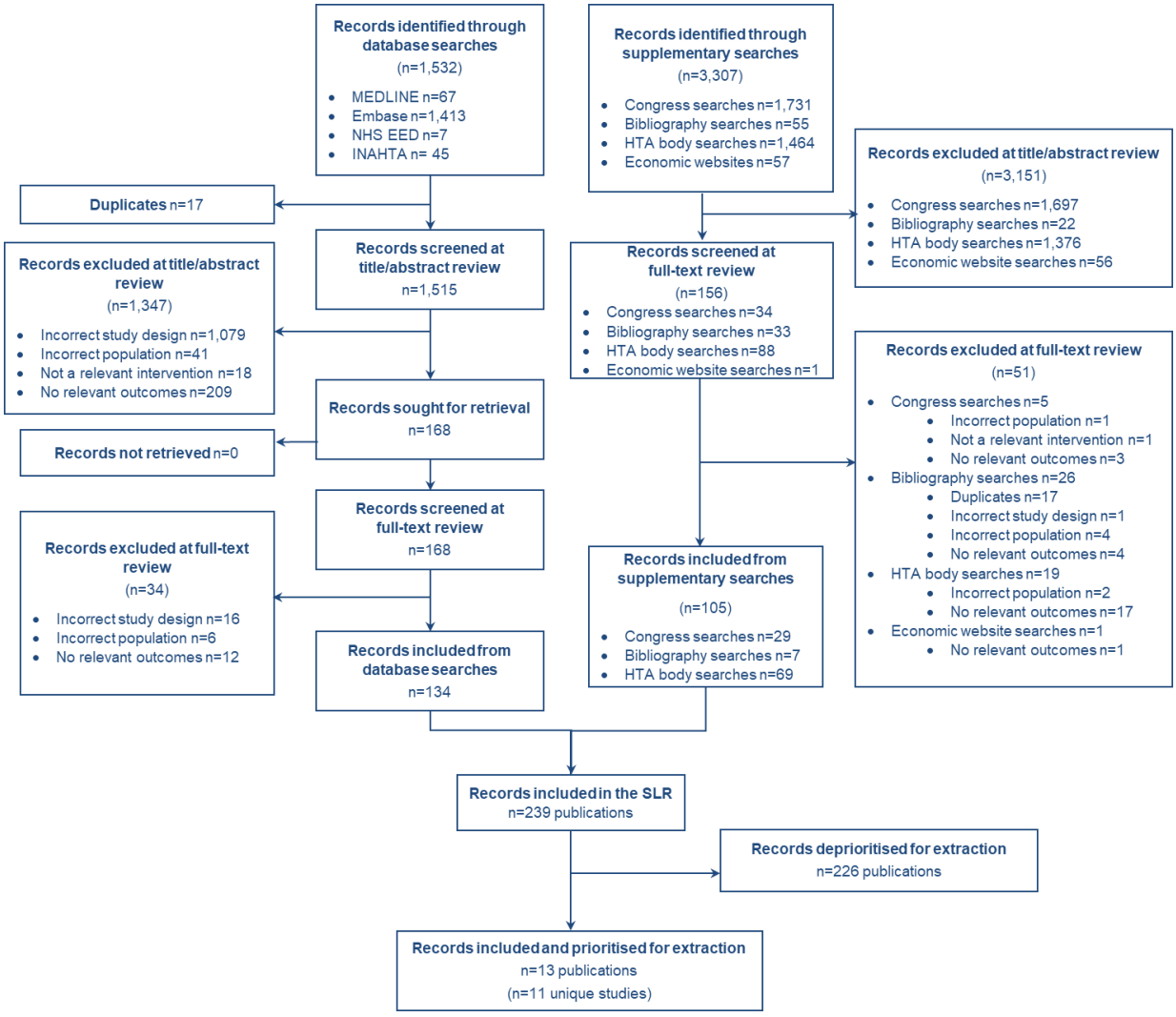
J&J IM would like to clarify that the original SLR (that goes back to May 2020 and with the first update in January 2021) was conducted to specifically support the NICE submission for ciltacabtagene autoleucel (cilta-cel, and a CAR-T therapy) (terminated TA899). Previous exposure to BCMA or CAR-T was an exclusion criterion for CARTITUDE-1 and, as such, SLR was aligned with these criteria. The SLR was subsequently updated and repurposed to support teclistamab (TA1015) and talquetamab submissions, in which previous exposure to TCR (including BCMA therapies) could be relevant, and therefore the SLR eligibility criteria was reviewed and adjusted. The revised PICO was applied from the February 2023 update onwards, covering the review period from April 2022 to current date, with studies on this emergent subgroup of patients captured and relevant studies included.

C9. For the SLR of cost-effectiveness evidence, please clarify the number of records identified through supplementary searches that were screened and excluded at the full text review, as illustrated in the PRISMA diagram (Appendix E.2, Figure 13). 3,307 records identified, minus 3,150 excluded at title/abstract review should leave 157 records for screening at full text review (not 56 as in the PRISMA diagram). If 51 were then excluded at full text review stage, 106 records would be included from the

supplementary searches (not 105). Additionally, please re-write the third paragraph of Appendix E.2, which contains several errors regarding the numbers of records retrieved and their sources

J&J IM would like to clarify that the PRISMA has been updated with the correct number of records identified and screened through the supplementary searches ('56' has been corrected to '156'), and the total number of records excluded from bibliography searches at the full-text stage has been corrected to 26. The updated PRISMA is presented below (Figure 20). The accompanying text has also been updated in the full appendices.

Figure 20. Economic SLR PRISMA flow diagram



Abbreviations: HTA: Health Technology Assessment; INAHTA: International Network of Agencies for Health Technology Assessment; NHSEED: National Health Service Economic Evaluation Database; SLR: systematic literature review.

‘A total of 1,532 citations were retrieved from the database searches conducted on 11th December 2024. After removing duplicates, 1,515 records remained and were screened at the title and abstract stage. Of these, 1,347 were excluded. Full texts (published articles and conference abstracts) of the remaining 168 records were obtained and assessed for eligibility. A total of 34 records were excluded for various reasons, as shown in the PRISMA flow diagram (Figure 20).

A total of 3,307 abstracts were identified through targeted grey literature searches of selected conferences. Of these, 156 records were deemed eligible for further screening. HTA searches identified 69 relevant records. A search of relevant congresses identified 29 records. Searching the bibliographies of on-topic SLRs that were identified in the database searches revealed seven additional records (105 included records from the supplementary searches, in total).

Subsequently, 239 publications in total met the inclusion criteria, including 139 published economic evaluations/HTA submission reports or BIMs, and 103 publications reporting cost and resource use/treatment pattern data. Thirty-three publications reported on economic data in a TCE RRMM population.

Ultimately, 13 publications (reporting on 11 unique studies) reported on talquetamab or teclistamab (the relevant comparator for this submission), and were prioritised for data extraction. However, as noted in Section 3.2 of the Company submission, no relevant economic evaluations comparing talquetamab to teclistamab from a UK perspective were identified in the SLR. Therefore, a *de novo* cost utility analysis was conducted for the purpose of the evaluation (see Section 3.2 for further details).’

C10. Please provide lists of publications identified through supplementary searches (congresses, HTA bodies, bibliographies and websites), but excluded at full text review from the cost effectiveness and health-related quality of life SLRs. Appendix E.21 Table 37 and Appendix F2 Table 48 only list the records excluded at full-text review identified via database searches (34 and 47 publications respectively)

The excluded records at the full text review from the supplementary searches are provided in Table 10 below, for the HRQoL SLR and in Table 11 for the economic SLR.

Table 10. Excluded records at the full-texts from the supplementary searches in the HRQoL SLR

#	Reference (RefID)	Source	Reason for Exclusion
1	Rong, R. et al. Cost-Effectiveness of Talquetamab-tgvs Vs Idecabtagene Vicleucel for Triple-Class Exposed Relapsed or Refractory Multiple Myeloma. Value in Health 2024;27(6):S10	Congress searches	No relevant outcomes
2	Su, W et al. Adjusting Utilities Using Age and Time-to-Death Decrements in Cost-Effectiveness Analyses: A Case Study in Relapsed and/or Refractory Multiple Myeloma. Value in Health 2024;27(6):S259	Congress searches	No relevant outcomes
3	Moreau, P. et al. (2023). P979: Patient-Reported Outcomes For Teclistamab Versus Real-World Physician's Choice Of Therapy In The Locommotion Study In Patients With Triple-Class Exposed Relapsed/Refractory Multiple Myeloma. HemaSphere 2023;7(Suppl):e690758f.	Congress searches	Irrelevant study design
4	Li, X. et al. Trajectories Of Patient-Reported Outcomes After Idecabtagene Vicleucel Vs. Ciltacabtagene Autoleucel Car T-Cell Therapy Among Patients With Relapsed/Refractory Multiple Myeloma In Standard Of Care. Blood 2024;144 (Supplement 1):7842	Congress searches	No relevant outcomes
5	Korsos V, Lobaugh SM, Sukhu R, Devlin SM, Atkinson T, Kemeny E, Stetson P, Perales MA, Giralt SA, Scordo M, Shah GL. Standard of care electronic patient-reported outcomes using PROMIS-29 after hematopoietic stem cell transplant and chimeric antigen receptor T cell therapy. Transplant Cell Ther. 2024;30(2 Suppl):S348.	Congress searches	Incorrect population
6	NICE 2024. Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments	HTA searches	No relevant outcomes (utilities redacted)

7	SMC 2024. Elranatamab (Elrexfio)	HTA searches	No relevant outcomes
8	SMC 2024. Teclistamab (Tecvayli)	HTA searches	No relevant outcomes
9	PBAC 2008. Lenalidomide	HTA searches	No relevant outcomes
10	PBAC 2018. DENOSUMAB, injection, 120 mg in 1.7 mL vial, Xgeva®, Amgen Australia Pty Ltd	HTA searches	Irrelevant population
11	CMA-AMC 2024. Talquetamab	HTA searches	No relevant outcomes
12	CMA-AMC. Velcade for Multiple Myeloma - Details	HTA searches	Irrelevant population
13	CMA-AMC 2024. Teclistamab	HTA searches	No relevant outcomes (utilities redacted)
14	IQWIG 2024. Elranatamab (multiple myeloma) Benefit assessment according to §35a SGB V1	HTA searches	No relevant outcomes
15	IQWIG 2022. Melphalan flufenamide (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
16	IQWIG 2017. Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
17	IQWIG 2021. Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
18	IQWIG 2022. Selinexor (multiple myeloma, ≥ 4 prior therapies) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
19	IQWIG 2019. Pomalidomide (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
20	IQWIG 2024. Idecabtagene vicleucel (multiple myeloma, ≥ 2 prior therapies) Benefit assessment according to §35a SGB V1	HTA searches	No relevant outcomes

21	IQWIG 2022. Selinexor (multiple myeloma, ≥ 1 prior therapy) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
22	IQWIG 2021. Isatuximab (multiple myeloma after ≥ 2 prior therapies) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
23	IQWIG 2021. Isatuximab (multiple myeloma, after ≥ 1 prior therapy) – Benefit assessment according to §35a Social Code Book V1 (early benefit assessment)	HTA searches	No relevant outcomes
24	IQWIG 2015. Pomalidomide – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
25	IQWIG 2016. Ibrutinib – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
26	ICER 2016. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma: Effectiveness and Value; Model Analysis Plan. Available at: https://osf.io/vtjda/	HTA searches	No relevant outcomes
27	ICER 2020. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma: Final Report. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_Multiple-Myeloma_Final-Report_Update_06092022.pdf	HTA searches	No relevant outcomes
28	CADTH 2022. Idecabtagene Vicleucel. Available at: https://www.cadth.ca/sites/default/files/DRR/2022/PG0240-Abecma.pdf	HTA searches	No relevant outcomes
29	CADTH 2016. Daratumumab. Available at: https://www.cadth.ca/sites/default/files/pcodr/pcodr_daratumumab_darzalex_mm_fn_egr.pdf	HTA searches	No relevant outcomes
30	ICER 2016. Multiple Myeloma: Model Analysis Plan. Available at: https://icer-review.org/material/multiple-myeloma-model/	HTA searches	No relevant outcomes
31	PBAC 2016. Carfilzomib. Available at : https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/carfilzomib-psd-november-2016.pdf	HTA searches	No relevant outcomes
32	PBAC 2020. Plitidepsin. Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-03/files/plitidepsin-psd-march-2020.pdf	HTA searches	No relevant outcomes

33	IQWiG 2021. Carfilzomib. Available at: IQWiG Carfilzomib	HTA searches	No relevant outcomes
34	IQWiG 2016. Elotuzumab. Available at: https://www.iqwig.de/download/a16-66_elotozumab_addendum-to-commission-a16-32_v1-0.pdf	HTA searches	No relevant outcomes
35	CADTH 2019. Pomalidomide in second line and beyond. Available at: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10165PomalidomideBortezomibMM_fnRec_EarlyConv_18Sep2019_final.pdf	HTA searches	No relevant outcomes
36	CADTH 2016. Ixazomib. Available at: https://www.cadth.ca/sites/default/files/pcodr/pcodr_ixazomib_ninlaro_mm_fn_rec.pdf	HTA searches	No relevant outcomes
37	CADTH 2022. Isatuximab (1-3 prior lines of therapy). Available at: https://www.cadth.ca/sites/default/files/DRR/2022/PC0256-Sarclisa-CombinedReport.pdf	HTA searches	No relevant outcomes
38	CADTH 2021. Isatuximab (in combination with Pomalidomide and Dexamethasone). Available at: https://www.cadth.ca/sites/default/files/pcodr/Reviews2021/10220IsatuximabMM_inEGR_NOREDACT-ABBREV_Post04Feb2021_final.pdf	HTA searches	No relevant outcomes
39	NICE 2009. Lenalidomide for two prev treatment Available at: https://www.nice.org.uk/guidance/ta171/documents/multiple-myeloma-lenalidomide-final-appraisal-determination3	HTA searches	No relevant outcomes
40	SMC 2014. Lenalidomide. Available at: https://www.scottishmedicines.org.uk/media/1909/lenalidomide__revlimid__2nd_resubmission_final_march_2014_amended_040414_for_website.pdf	HTA searches	No relevant outcomes
41	SMC 2009. Pegylated liposomal doxorubicin (Caelyx). Available at: https://www.scottishmedicines.org.uk/media/2138/pegylated_liposomal_doxorubicin__caelyx__resubmission__final_june_2009_for_website.pdf	HTA searches	No relevant outcomes
42	NICE 2021. Carfilzomib in combination with dexamethasone and lenalidomide. Available at: https://www.nice.org.uk/guidance/ta695/documents/final-appraisal-determination-document	HTA searches	No relevant outcomes

43	PBAC 2020. Pomalidomide. Available at : https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-03/files/plitidepsin-psd-march-2020.pdf	HTA searches	No relevant outcomes
44	CADTH 2019. Ixazomib in second line and beyond. Available at: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10164IxazomibMM_fnRec_2019-07-05_ChairApproved_Post_05Jul2019_final.pdf	HTA searches	No relevant outcomes
45	CADTH 2016. Carfilzomib (with lenalidomide). Available at: https://www.cadth.ca/sites/default/files/pcodr/pcodr_carfilzomib_kyprolis_mm_fn_egr.pdf	HTA searches	No relevant outcomes
46	Institute for Clinical and Economic Review. Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks: Evidence Review Report 2016. Available at: https://icer.org/wp-content/uploads/2020/10/MWCEPAC_MM_Evidence_Report_050516-1.pdf	Economic websites	No relevant outcomes
47	Neves, M., Trigo, F., Rui, B., et al. Multiple Myeloma in Portugal: Burden of Disease and Cost of Illness. Pharmacoeconomics. 2021;39(5):579-587	Economic websites	No relevant outcomes
48	Delforge, M., Dhawan, R., Robinson, D Jr, Meunier, J., Regnault, A., Esseltine, D.L., et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. European Journal of Haematology 2012;89(1):16-27.	Bibliography searches	Incorrect population
49	Mellqvist, U.H., Gimsing, P., Hjertner, O., LenhoK, S., Laane, E., Remes, K., et al. Bortezomib consolidation aTer autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood 2013;121(23):4647-54.	Bibliography searches	Incorrect population

Table 11. Excluded records at the full text review from the supplementary searches in the economic SLR

#	Reference (RefID)	Source	Reason for Exclusion
1	Farghaly, M et al. EE178 The Burden of Multiple Myeloma in the Gulf Region. Value in Health 2024;27(12):S88	Congress searches	Irrelevant/no intervention

2	Hellem Schjesvold, F. et al. EE73 Ocean (OP-103): Patients with Relapsed/Refractory Multiple Myeloma Treated with Melflufen Plus Dexamethasone or Pomalidomide Plus Dexamethasone - a Resource Utilization Analysis of Adverse Events Leading to Hospitalizations. Value in Health 2023;26(12):S64	Congress searches	No relevant outcomes
3	Sidana, S., Thirumalai, D., Itani, T., Baro, E., Giordana, M., Granados, E., Hasegawa, K., Rosado, M. B. Treatment Patterns And Outcomes In Triple-Class Exposed Patients With Relapsed And Refractory Multiple Myeloma: Findings From The Flatiron Database. Blood 2024:144 (Supplement 1):6962	Congress searches	No relevant outcomes
4	Gregory, T., Blunk, B., Cox, T., Billups, R., Mattlin, M., Martin, C., Berdeja, J. G., Bhushan, V., LeMaistre, C. F., Ramakrishnan, A., Shaughnessy, P. J., Majhail, N. S., Battiwalla, M. Carvykti (cilta-cel) Real World Outcomes across the Sarah Cannon Transplant Cell Therapy Network, Transplantation and Cellular Therapy 2024;30(2, Supplement): S385-S386	Congress searches	Incorrect population
5	Schinke, C., Dhakal, B., Mazzoni, S., Shenoy, S., Scott, S., Richards, T., Le, H., DeBrosse, A., Okorozo, P., McDowell, R., Patel, S., Bunn, J., Hawks, K., Zhang, X., Rodriguez-Valdes, C. Real-World Experience With Talquetamab Clinical Management In Relapsed Refractory Multiple Myeloma (RRMM): A Qualitative Study Of Us Healthcare Providers. 21st International Myeloma Society Annual Meeting September 2024 Abstract Book:S265-266	Congress searches	No relevant outcomes
6	PBAC 2008. Lenalidomide. Available at: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-lenalidomide-nov08	HTA searches	No relevant outcomes
7	PBAC 2018. DENOSUMAB, injection, 120 mg in 1.7 mL vial, Xgeva®, Amgen Australia Pty Ltd. Available at: https://m.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-11/Denosumab-psd-november-2018.html	HTA searches	Incorrect population
8	CDA-AMC 2013. Velcade for Multiple Myeloma – Details. Available at: https://www.cda-amc.ca/velcade-multiple-myeloma-details	HTA searches	Incorrect population
9	IQWIG 2024. Elranatamab (multiple myeloma) Benefit assessment according to §35a SGB V1	HTA searches	No relevant outcomes

10	IQWIG 2022. Melphalan flufenamide (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
11	IQWIG 2017. Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
12	IQWIG 2021. Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
13	IQWIG 2022. Selinexor (multiple myeloma, ≥ 4 prior therapies) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
14	IQWIG 2019. Pomalidomide (multiple myeloma) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
15	IQWIG 2024. Idecabtagene vicleucel (multiple myeloma, ≥ 2 prior therapies) Benefit assessment according to §35a SGB V1	HTA searches	No relevant outcomes
16	IQWIG 2022. Selinexor (multiple myeloma, ≥ 1 prior therapy) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
17	IQWIG 2021. Isatuximab (multiple myeloma after ≥2 prior therapies) – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
18	IQWIG 2021. Isatuximab (multiple myeloma, after ≥1 prior therapy) – Benefit assessment according to §35a Social Code Book V1 (early benefit assessment)	HTA searches	No relevant outcomes
19	IQWIG 2015. Pomalidomide – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
20	IQWIG 2016. Ibrutinib – Benefit assessment according to §35a Social Code Book V1	HTA searches	No relevant outcomes
21	NICE 2017. Carfilzomib for previously treated multiple myeloma (TA457) Available at: https://www.nice.org.uk/guidance/ta457/documents/committee-papers	HTA searches	No relevant outcomes
22	NICE 2018. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). Available at:	HTA searches	No relevant outcomes

	https://www.nice.org.uk/guidance/ta510/documents/committee-papers		
23	NICE 2019. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). Available at: https://www.nice.org.uk/guidance/ta573/documents/committee-papers	HTA searches	No relevant outcomes
24	NICE 2018. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). Available at: https://www.nice.org.uk/guidance/ta505/documents/committee-papers	HTA searches	No relevant outcomes
25	Neves, M., Trigo, F., Rui, B., et al. Multiple Myeloma in Portugal: Burden of Disease and Cost of Illness. Pharmacoeconomics. 2021;39(5):579-587	Economic websites	No relevant outcomes
26	Canadian Agency for Drugs and Technologies in Health (CADTH). Pomalyst in combination with dexamethasone and bortezomib for multiple myeloma (second-line or beyond) (PC0165-000). 2019. Available from: https://www.cadth.ca/pomalyst-combination-dexamethasone-and-bortezomib-multiple-myeloma-second-line-or-beyond-details. Accessed 7 Sep 2023.	Bibliography searches	No relevant outcomes
27	Canadian Agency for Drugs and Technologies in Health (CADTH). Selinexor (PC0276-000). 2022. Available from: https://www.cadth.ca/selinexor. Accessed 7 Sep 2023.	Bibliography searches	No relevant outcomes
28	Exploring the cost of care at the end of life. Nuffield Trust; https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life	Bibliography searches	Irrelevant study design
29	Goodwin JA, Coleman EA, Sullivan E, Easley R, McNatt PK, Chowdhury N, et al. Personal financial effects of multiple myeloma and its treatment. Cancer Nurs 2013;36(4):301-8.	Bibliography searches	Incorrect population
30	Henk HJ. Health care costs and resource utilization, including patient burden, associated with novel-agent-based treatment versus other therapies for multiple myeloma: findings using real-world claims data. Oncologist. 2013;18:37-45.	Bibliography searches	Incorrect population
31	Pharmaceutical Benefits Advisory Committee (PBAC). 7.10 Selinexor, tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd. (March 2022). 2022. Available from:	Bibliography searches	No relevant outcomes

	https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/fles/selinexor-rr-mm-psd-march-2022.pdf. Accessed 7 Sep 2023.		
32	Yong, K., Delforge, M., Driessen, C., Fink, L., Flinois, A., Gonzalez-McQuire, S., Safaei, R., Karlin, L., Mateos, M.-V., Raab, M.S., Schoen, P. and Cavo, M. (2016), Multiple myeloma: patient outcomes in real-world practice. Br J Haematol, 175: 252-264. https://doi.org/10.1111/bjh.14213	Bibliography searches	Incorrect population
33	Zheng B, Reardon PM, Fernando SM, et al. Costs and outcomes of patients admitted to the intensive care unit with cancer. J Intensive Care 2021;36(2):203-210	Bibliography searches	Incorrect population
34	Pharmaceutical Benefts Advisory Committee (PBAC). 7.13 Pomalidomide, capsule 3 mg, 4 mg, Pomalyst®, Celgene Pty Ltd. (November 2019). 2019. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-11/fles/pomalidomide-psd-november-2019.pdf. Accessed 7 Sep 2023	Bibliography searches	No relevant outcomes
35	Canadian Agency for Drugs and Technologies in Health (CADTH). Isatuximab (PC0256-000). 2022. Available from: https://www.cadth.ca/isatuximab. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
36	National Institute for Health and Care Excellence (NICE). Carfilzomib for previously treated multiple myeloma (TA657). 2020. Available from: https://www.nice.org.uk/guidance/ta657/. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
37	National Institute for Health and Care Excellence (NICE). Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy (TA695). 2021. Available from: https://www.nice.org.uk/guidance/ta695/. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
38	National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). 2019. Available from: https://www.nice.org.uk/guidance/ta171/. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches

39	National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (TA586 [partial review of TA171]). 2019. Available from: https://www.nice.org.uk/guidance/ta586/. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
40	Pharmaceutical Benefits Advisory Committee (PBAC). 5.07 Ixazomib, capsule 2.3 mg, capsule 3 mg, capsule 4 mg, Ninlaro®, Takeda Pharmaceuticals Australia Pty Ltd. (November 2020). 2020. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-11/files/ixazomib-psd-nov-2020.pdf. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
41	Pharmaceutical Benefits Advisory Committee (PBAC). 5.07 Selinexor, tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd. (July 2021). 2021. Available from: https://www.pbs.gov.au/ industry/listing/elements/pbac-meetings/psd/2021-07/fles/ selinexor-RRMM-psd-july-2021.pdf. Accessed 7 Sep 2023	Bibliography searches	Duplicate with HTA searches
42	Pharmaceutical Benefits Advisory Committee (PBAC). 5.08 Selinexor, tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd. (July 2021). 2021. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-07/files/selinexor-TCR-PR-MM-psd-july-2021.pdf. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
43	Pharmaceutical Benefits Advisory Committee (PBAC). 6.08 Carfilzomib, powder for injection 10 mg, 30 mg and 60 mg, Kyprolis®, Amgen Australia Pty Limited. (July 2020). 2020. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-07/files/carfilzomib-psd-july-2020.pdf. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
44	Pharmaceutical Benefits Advisory Committee (PBAC). 7.01 daratumumab, solution concentrate for I.V. infusion, 100 mg in 5 mL, 400 mg in 20 mL, Darzalex®, Janssen-Cilag Pty Ltd. (November 2019). 2019. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-11/files/daratumumab-psd-november-2019.pdf. Accessed 7 Sep 2023.	Bibliography searches	Duplicate with HTA searches
45	Pharmaceutical Benefits Advisory Committee (PBAC). 7.03 daratumumab, solution concentrate for I.V. infusion 100 mg in 5 mL, 400 mg in 20 mL, Darzalex®, Janssen-Cilag Pty Ltd. (March 2019). 2019. Available from: https://www.pbs.gov.au/industry/listing/elements/p	Bibliography searches	Duplicate with HTA searches

	bac-meetings/psd/2019-03/files/daratumumab-psd-march-2019.pdf. Accessed 7 Sep 2023.		
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Missing textual detail and typos in text

C11. On page 77 of the CS Section 2.6.8, the company state "*Please note that the write-up of PRO data from the* September *2024 DCO was not available in time for the submission deadline and therefore not presented in this section. It will be provided as an addendum when possible."*

Please provide this missing information as part of the clarification response.

A summary of the PRO data from the September 2024 DCO has been supplied as an addendum along with this response.

C12. Several statements in the CS refer to "Advice from UK clinical experts" (Table 1, pg 13, Section 1.3 pg 20, etc). Please provide the name, role and conflict of interest declaration for these experts, and how they contributed advice – e.g., via survey, face to face consultation etc.

As noted in the Company response to B10, the advisory board report has been provided as part of the reference pack alongside the CQ responses. Whilst the names and roles of these experts have not been provided for these experts, all payments made as part of the advisory board are publicly disclosed according to the ABPI code and advisors will be required to declare any conflicts at a future committee meeting if relevant.[29]

C13. Appendix B.1.6, page 108: Figures 6-9 are incorrect and should be changed to 8-11, please correct them individually in text on page 108

J&J acknowledge this oversight, an updated version of the Appendices with the corrected Figure numbers have been supplied as part of this response.

C14. In Table 14, page 66. There is a double entry of the same item #20.

J&J acknowledge this oversight, an updated version of the Evidence Submission with the corrected Table 14 has been supplied as part of this response.

C15. On page 165, the company stated that *'The total cost across adverse events included in the model was £[redacted] for talquetamab and £[redacted] for teclistamab, respectively.'* Please can the company clarify if these results should have been confidentiality marked?

J&J IM extends their appreciation to the EAG for picking up this oversight and can confirm that these results should both be confidentiality marked. As noted in the Company response to B22, the total AE costs should be £[redacted] and £[redacted] following the correction to the percentage of patients receiving teclistamab experiencing hypokalaemia to [redacted]% from its previous value of [redacted]%.

J&J IM would like to request the EAG to update the clarification question accordingly, as follows: "*'The total cost across adverse events included in the model was* [redacted] *for talquetamab and* [redacted] *for teclistamab, respectively.'*"

Updated versions of the Appendices and the Company Evidence Submission with the corrected AE costs marked with the appropriate confidentiality marking have been provided alongside this response.

Appendices

Appendix A

The clinical parameters informing the extrapolation and modelling of teclistamab

The following appendix describes the NICE committee accepted approach to the survival extrapolations of teclistamab in TA1015, in response to clarifications B5 and B6.[23]

Despite having extensive trial and study follow-up data, the follow-up period for MajesTEC-1 was shorter than the model time horizon (40 years) and extrapolations of the observed OS, PFS (using time to next treatment [TTNT] as a proxy) and TTD data were required. In TA1015, time to next treatment [TTNT] was used a proxy for PFS in the absence of PFS data available for the comparator, pomalidomide plus dexamethasone (PomDex) from the efficacy data source, the UK real-world (RW) triple-class exposed (TCE) cohort study. However, in the ingoing submission, given the availability of PFS data for both teclistamab and talquetamab, PFS extrapolations were fitted to PFS data from MajesTEC-1 adjusted to match MonumenTAL-1.

In accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 guidance, a range of standard parametric distributions (e.g., exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored.[30] Each model was assessed in terms of goodness-of-fit statistics (Akaike information criterion [AIC] and the Bayesian information criteria [BIC]), visual inspection of the hazard function and survival extrapolations versus the observed data in the MajesTEC-1 trial and clinical plausibility of long-term survival predictions.

Overall survival

In TA1015, extrapolations were fitted to the OS data from MajesTEC-1 adjusted to match the UK RW TCE cohort study (as detailed in the ITC comparing teclistamab and pomalidomide plus dexamethasone [PomDex] in TA1015) and additionally adjusted to account for subsequent treatments not routinely available in the UK.[23] This two-stage OS adjustment used the same approach as the one described in the CS for talquetamab.

Mortality for patients with MM is expected to be higher than the mortality of the general population when matched for age and gender, so to ensure that the hazard of death was at least equal to GPM at any timepoint, age- and gender-matched GPM (based on life tables for England from the Office for National Statistics 2018-2020) was used in any cycle where the predicted rate of death was lower than general population mortality.[31]

In TA1015, the LogNormal and Generalised gamma extrapolations provided the best statistical fit to the observed OS data with respect to AIC and BIC.[23] However, despite adjusting for subsequent treatments not routinely commissioned in the UK, none of the generated extrapolations appeared to be suitable for use in the base case economic analysis when both statistical fit and long-term clinical plausibility were considered together. As such, the LogNormal extrapolation was subsequently calibrated to align to the clinically plausible estimates for long-term survival for teclistamab. This was considered to be the most appropriate approach with both high internal (statistical fit) and external (clinical plausibility) validity.

After Year 5 in the model, an attenuation factor was derived using a standardised mortality ratio factor applied to the general population mortality, as detailed in clarification B4 of this response. The resulting calibrated LogNormal extrapolation thus provided the best fit to the observed MajesTEC-1 trial data while also ensuring that the long-term survival extrapolations remain in line with clinical expectations and was therefore selected.[23] This extrapolation, which was accepted by the NICE committee in TA1015, is presented in Figure 21.[23]

Figure 21: Attenuated log-normal OS extrapolation for teclistamab fitted to the subsequent treatment adjusted OS KM data from MajesTEC-1; adjusted via IPTW using ATC weights to align with the UK RW TCE cohort study

Footnotes: Clinical expert feedback was sought at 5-, 10- and 15- year timepoints.
Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Progression-free survival

Extrapolations were fitted to the TTNT data (as a proxy for PFS) from MajesTEC-1 adjusted to match the UK RW TCE cohort study (as detailed in the ITC comparing teclistamab and [PomDex] in TA1015).[23] The PFS extrapolations implemented in the model include a cap to ensure that PFS did not exceed OS for teclistamab to ensure clinical plausibility.

Similar to OS, the Generalised Gamma and LogNormal extrapolations provided the best statistical fit to the observed data according to AIC and BIC statistics, respectively, while the LogNormal extrapolation provided more clinically plausible long-term PFS estimates. In line with the approach taken for OS, after Year 5, an attenuation factor was applied to the LogNormal extrapolation to increase the hazard of disease progression in each cycle after Year 5, so that the log-normal extrapolation resulted in a 10-year PFS of 5% (the midpoint of 2-8%) and a 15-year PFS of 1% (the midpoint of 0-2%).

The resulting calibrated LogNormal PFS extrapolation showed both high internal validity with the best statistical fit to the MajesTEC-1 PFS data, as well as high external validity and was therefore selected, and accepted by the EAG in TA1015.[23] This extrapolation, which was approved by the NICE committee in TA1015 is presented in Figure 22.[23]

Figure 22: Attenuated log-normal PFS extrapolation for teclistamab fitted to the TTNT KM data from MajesTEC-1; adjusted via IPTW using ATC weights to align with the UK RW TCE cohort study

Footnotes: Clinical expert feedback was sought at 5-, 10- and 15- year timepoints.
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Time to treatment discontinuation

In order to model treatment duration for teclistamab, extrapolations were fitted to TTD data from MajesTEC-1.[23] The log-normal extrapolation provided the best statistical fit, followed by the generalised gamma extrapolation. However, the long-term estimates of TTD associated with the log-normal, generalised gamma, log-logistic and Gompertz extrapolations all exceeded the upper range of the clinical expert estimates for both 10- and 15- years, meaning all four extrapolations were considered to lack external validity, and were ruled out as being clinically implausible.[23]

The EAG ultimately selected the LogNormal distribution for consistency with the curve selection for OS and PFS, and calibrated this to the clinical estimates for TTD, in alignment with the approach for OS and PFS. This calibration was conducted using the same methodology outlined above for OS and PFS. The committee in TA1015 subsequently accepted the calibrated LogNormal distribution as the extrapolation of TTD for teclistamab.[23]

Appendix B

Corrected base case and scenario analyses results

As mentioned in response to B20, updated versions of the Company Submission documents (Evidence Submission, Appendices, Cost-Effectiveness Model and Budget Impact Analysis document) have been provided alongside the CQ response to reflect the corrected value for hypokalaemia incidence with teclistamab in MajesTEC-1 (the value was updated from [redacted]% to [redacted]%). The corrected results are also presented below.

Additionally, as detailed in response to B17, J&J IM have included three additional scenario analyses to account for the costs associated with IVIg use with subsequent teclistamab following talquetamab treatment.

Please note that the additional scenarios modelling IVIg use for subsequent teclistamab treatment have not been included in the accompanying Evidence Submission document as they

do not represent a correction to the previously submitted document, and the results of these scenarios are presented below in Table 16.

Base case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness results for talquetamab versus teclistamab, both at list price and with-PAS price, are presented in Table 12 and Table 13, respectively. The probabilistic base case cost-effectiveness results, both at list price and with-PAS price, are presented in Table 14 and Table 15, respectively.

Table 12: Deterministic base-case results (talquetamab and teclistamab list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.27	[redacted]					
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£64,459	-2.25

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 13: Probabilistic base-case results (talquetamab and teclistamab list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.34	[redacted]					
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£64,760	-2.32

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 14: Deterministic base-case results (talquetamab and teclistamab PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.27	[redacted]					
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£29,277	0.05

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 15: Probabilistic base-case results (talquetamab and teclistamab PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Talquetamab	[redacted]	6.34	[redacted]					

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£29,246	0.05

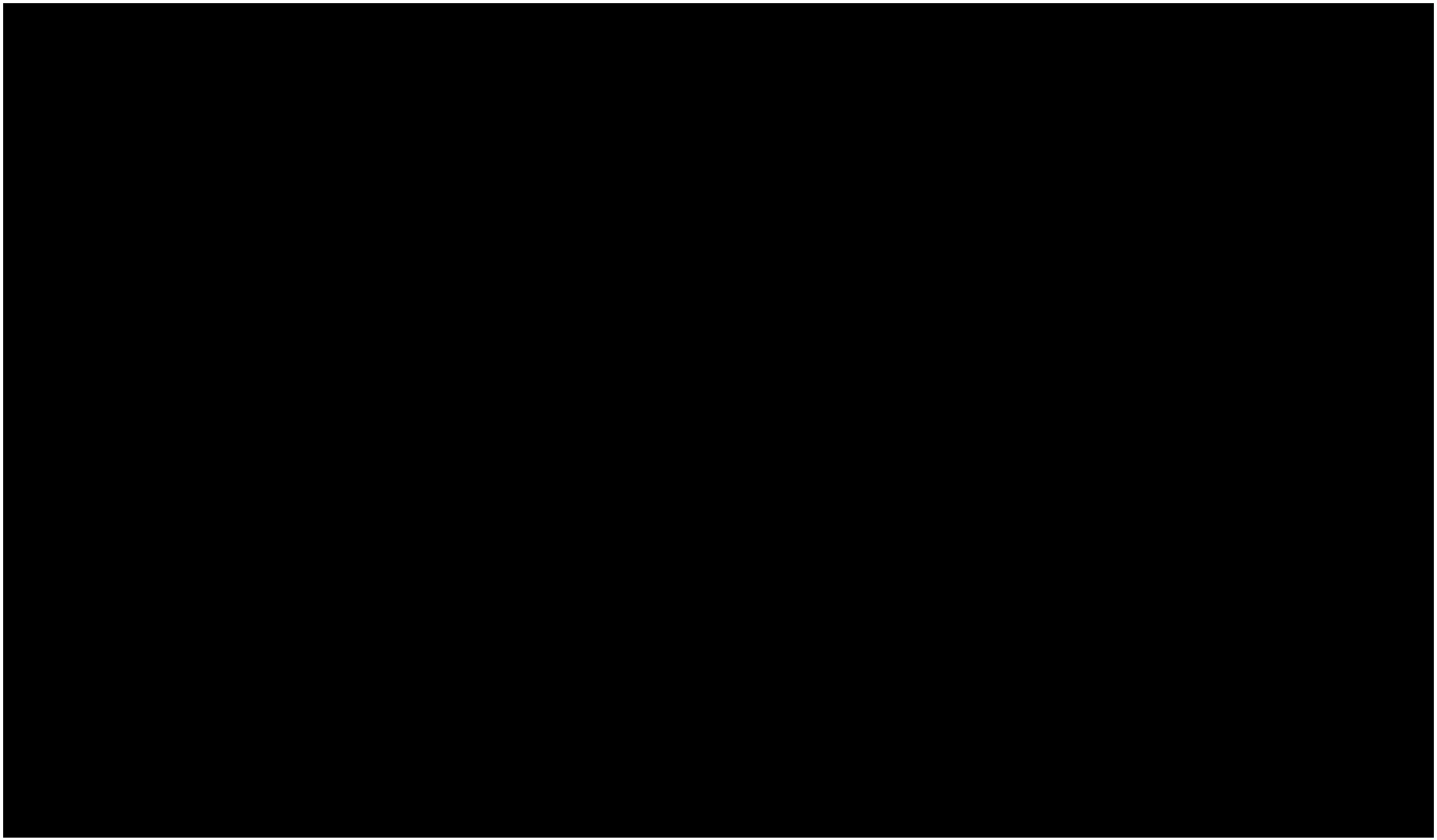
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Probabilistic sensitivity analysis

INHB convergence plots are provided for the with-PAS price of talquetamab and teclistamab in Figure 23 below. The plots demonstrate that the cumulative INHB converges after approximately 400 iterations for the with-PAS analysis.

The probabilistic cost-effectiveness planes for talquetamab (with-PAS) versus teclistamab (with-PAS) is presented in Figure 24. The cost-effectiveness acceptability plots are presented in Figure 25; the PSA found the probability of talquetamab being a cost-effective use of NHS resources to be [redacted] and [redacted] at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 23: INHB convergence plot (talquetamab and teclistamab PAS price)



Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme.

Figure 24: Probabilistic cost-effectiveness plane for talquetamab versus teclistamab (talquetamab and teclistamab PAS price)

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

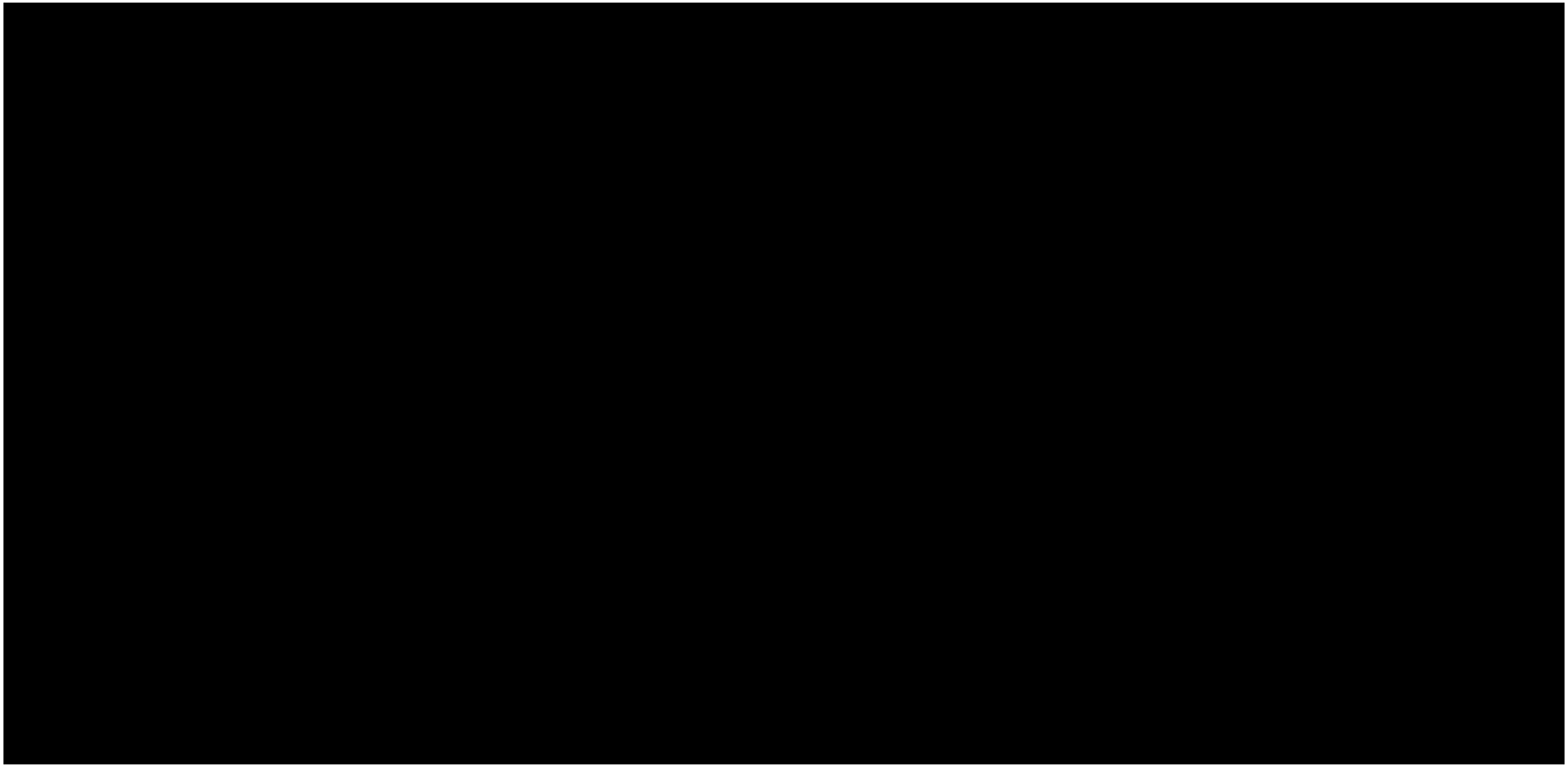
Figure 25: Cost-effectiveness acceptability curve for talquetamab versus teclistamab (talquetamab and teclistamab PAS price)

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; WTP: willingness-to-pay threshold.

Deterministic sensitivity analysis

A tornado diagram showing the top 10 most influential parameters on the incremental net health benefit (INHB) for talquetamab (with-PAS) versus teclistamab (with-PAS) is presented in Figure 26.

Figure 26: DSA tornado diagram for talquetamab versus teclistamab, INHB (talquetamab and teclistamab PAS price)



Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme; PFS: progression-free survival; PPS: post-progression survival SC: subcutaneous.

Scenario analysis

A summary of the deterministic scenario analysis results incorporating the PAS discounts for both talquetamab and teclistamab is presented in Table 16. This table includes the three additional scenarios accounting for IVIg use with the subsequent teclistamab treatment that were described in response to B17. The rationale for each of the other scenarios included is detailed in the CS, in Table 79 of Section 3.11.3.

Table 16: Summary of scenario analysis results (talquetamab and teclistamab PAS price) – deterministic

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Base case		[redacted]	[redacted]	£29,277	0.05
1a	Time horizon: 25 years	[redacted]	[redacted]	£29,561	0.03
1b	Time horizon: 30 years	[redacted]	[redacted]	£29,294	0.05
2	Talquetamab efficacy data source: Weighted split 90%/10% Cohort C and A	[redacted]	[redacted]	£29,580	0.03
3	Utility values: Derived from MajesTEC-1	[redacted]	[redacted]	£30,926	-0.06
4	AE disutilities: No decrements applied	[redacted]	[redacted]	£29,421	0.04
5	Subsequent treatment: Reweighting non-teclistamab subsequent treatment (i.e. 70%/20%/10% split for PomDex/PanBorDex/SelDex)	[redacted]	[redacted]	£31,175	-0.08
6a	Subsequent treatment: Removal of all non-routine UK treatment, as well as removing teclistamab from MonumenTAL-1 – All Out	[redacted]	[redacted]	£31,280	-0.07
6b	Subsequent treatment: Removal of all non-routine UK treatment, but allowing subsequent talquetamab following teclistamab, vice versa – All In	[redacted]	[redacted]	£29,109	0.06
7a	Talquetamab PFS/OS/TTD: Individually fitted Lognormal	[redacted]	[redacted]	£23,675	0.51
7b	Talquetamab PFS/OS/TTD: Individually fitted Weibull	[redacted]	[redacted]	£22,631	0.38
7c	Talquetamab PFS/OS/TTD: Individually fitted Gamma	[redacted]	[redacted]	£25,361	0.20
8a	Subsequent teclistamab IVIg dose of 3 months	[redacted]	[redacted]	£29,570	0.03
8b	Subsequent teclistamab IVIg dose of 6 months	[redacted]	[redacted]	£29,864	0.01
8c	Subsequent teclistamab IVIg dose of 9 months	[redacted]	[redacted]	£30,157	-0.01

Abbreviations: AE: adverse events; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; IVIg: intravenous immunoglobulin; OS: overall survival; PanBorDex: panobinostat with bortezomib and dexamethasone; PAS: patient access scheme; PFS: progression-free survival; PomDex: pomalidomide with dexamethasone; QALY: quality-adjusted life year; SelDex: selinexor with dexamethasone; TTD: time to treatment discontinuation; UK: United Kingdom.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082] Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID5082 Talquetamab Clarification response_C2 _090525_[no CON]	1.0	No	9th May, 2025

Section C: Textual clarification and additional points

C2. Appendix B.1.3 states "*A total of 6,588 citations were retrieved from the database searches conducted on 26th May 2020, 22nd January 2021, 27th April 2022, May 2022, February 2023 and October 2023*." However, the total numbers of results from searches recorded in tables 1-7 do not amount to 6,588.

Please explain this discrepancy and confirm whether the June 2021 update should also have been listed here

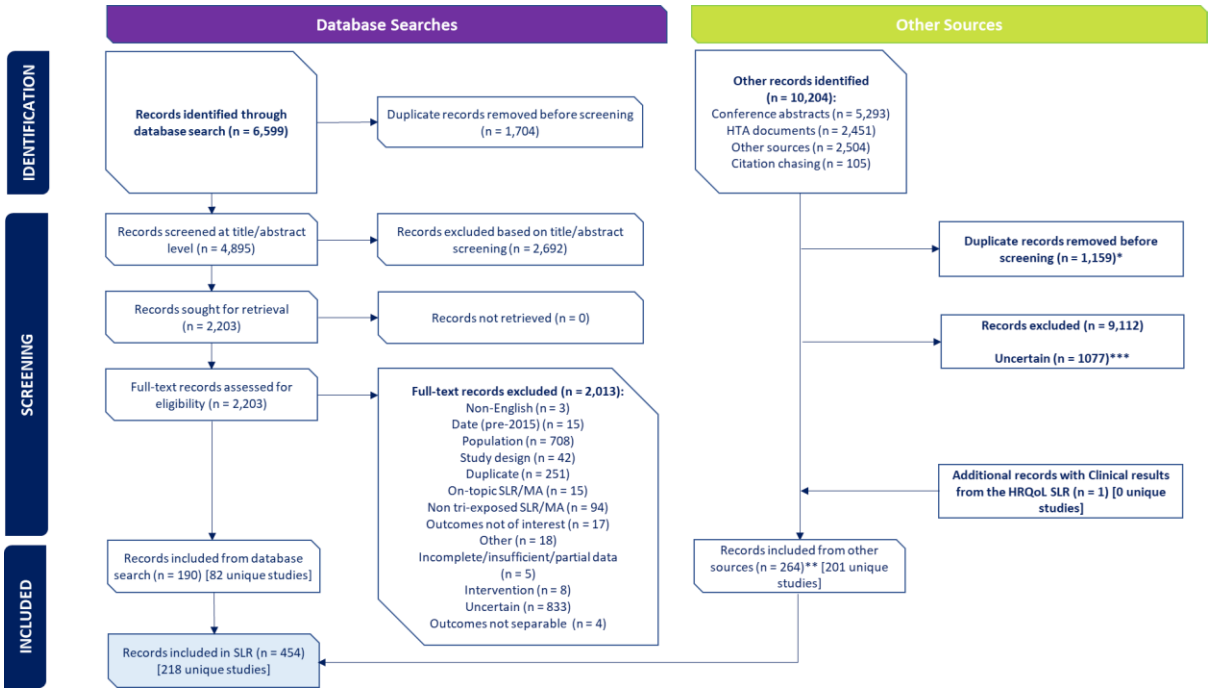
J&J IM can confirm that the June 2021 update should be listed in the text above.

In regard to the total number of results reported, J&J IM can confirm that the number of database search records between each update has been validated with each independent reviewer SLR team. The table below tracks the number of total records (before duplicate removal) identified through database searches.

	Database Search (**including** duplicates)	Cumulative number of records	Database Search Tables listed in the CS Appendix
May-2020	3843	3843	Table 1 - Row #69
January-2021 **(1st update)**	354	4197	Table 2 - Row #75
June-2021 **(2nd update)**	57	4254	Table 3 - Row #82
April-2022 **(3rd update)**	1313	5567	Table 4 - Row #76
May-2022 **(4th update)**	40	5607	Table 5 - Row #76
Feb-2023 **(5th update)**	611	6218	Table 6 - Row #74
Oct-2023 **(6th update)**	381	**6599**	Table 7 - Row #74

J&J IM would like to clarify that the correct total number of records (including duplicates) identified through database searches conducted in May 2020, January 2021, June 2021, April 2022, May 2022, February 2023 and October 2023 is **6599** records. The discrepancy between this record number (n=6599) and the number indicated in the original text and PRISMA flow diagram (n=6588) comes from a small error in duplicate removal counting; there is no impact on the screening phase.

Please find bellow the corrected PRISMA flow diagram for original SLR and updates up to October 2023.


Database Searches
Other Sources
IDENTIFICATION
SCREENING
INCLUDED
Records identified through database search (n = 6,599)
Duplicate records removed before screening (n = 1,704)
Other records identified (n = 10,204):
Conference abstracts (n = 5,293)
HTA documents (n = 2,451)
Other sources (n = 2,504)
Citation chasing (n = 105)
Records screened at title/abstract level (n = 4,895)
Records excluded based on title/abstract screening (n = 2,692)
Duplicate records removed before screening (n = 1,159)*
Records sought for retrieval (n = 2,203)
Records not retrieved (n = 0)
Records excluded (n = 9,112)
Uncertain (n = 1077)***
Full-text records assessed for eligibility (n = 2,203)
Full-text records excluded (n = 2,013):
Non-English (n = 3)
Date (pre-2015) (n = 15)
Population (n = 708)
Study design (n = 42)
Duplicate (n = 251)
On-topic SLR/MA (n = 15)
Non tri-exposed SLR/MA (n = 94)
Outcomes not of interest (n = 17)
Other (n = 18)
Incomplete/insufficient/partial data (n = 5)
Intervention (n = 8)
Uncertain (n = 833)
Outcomes not separable (n = 4)
Additional records with Clinical results from the HRQoL SLR (n = 1) [0 unique studies]
Records included from database search (n = 190) [82 unique studies]
Records included from other sources (n = 264)** [201 unique studies]
Records included in SLR (n = 454) [218 unique studies]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK focussed exclusively on myeloma and related conditions. Our broad and innovative range of services cover every aspect of living with myeloma, from diagnosis, treatment and care pathways to providing emotional and psychological support. We provide information and peer support for patients, families and carers living across the UK. We utilise our lived experience insights to improve healthcare experience and promote higher standards of treatment and care through our research, policy and campaigning activities. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have received funding from the manufacturer of the technology (J&J) in the last 12 months. In 2023, 6% of Myeloma UK's income came from pharmaceutical companies. The table below shows the 2023 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

	Core grant	Research / Project	Donation	Consultancy/ Honoraria	Events	Total
AbbVie Ltd	-	10,000	-	870	-	10,870
Alexion Pharma UK Ltd	-	7,500	-	-	-	7,500
Amgen Ltd	-	20,000	-	-	-	20,000
The Binding Site Ltd	20,000	-	-	437	-	20,437
Bristol-Myers Squibb Pharmaceuticals Ltd	15,000	-	-	-	-	15,000
GlaxoSmithKline UK Limited	-	20,026	-	-	-	20,026
ITECHO Health Ltd	-	6,600	-	-	-	6,600
Janssen-Cilag Ltd (now J&J)	-	15,907	-	260	9,093	25,260
Menarini Stemline UK Limited	-	7,000	-	-	-	7,000
Pfizer Limited	-	-	-	73,448	-	73,448
Stemline Therapeutics Switzerland GmbH	-	-	-	1,451	-	1,451
Sanofi	-	-	-	-	27,990	27,990

	Takeda UK	30,000	-	-	-	29,681	59,681
		65,000	**87,033**	**-**	**76,466**	**66,764**	295,263
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None						
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research and services programmes, including: - Semi-structured interviews in February-March 2025 with relapsed/refractory myeloma patients. These interviews provide valuable experience and insight data from patients who have had or are currently having talquetamab. - A Myeloma UK-funded, multi-criteria decision analysis study of 560 myeloma patients run by the European Medicines Agency (EMA) and the University of Groningen. The study explored patient preferences for different benefit and risk outcomes in myeloma treatment. - Analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays, posts to our online Discussion Forum, feedback from our Advocacy Partner Panel, myeloma UK peer support groups and insights gathered for earlier appraisals. - Discussion and interviews with clinicians, healthcare professionals and medical societies who manage diagnosis, treatment and care of people living with myeloma.						

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. Currently, there is no cure, but treatment can halt its progress and improve the quality of life. The complications of myeloma can be significant, debilitating, and painful; they include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. Complications which result from myeloma can drastically impact patients' quality of life. These can affect patients in different ways and can range from dramatic loss in height, serious fatigue, reduced appetite, breathing problems, reduced mobility and independence, and poorer mental health. ***"Living with myeloma is a monumental pain in the neck. It's quite difficult and its hugely variable of course. It is quite painful at times. The general feeling of wellness, is quite variable. Sometimes I feel fine, largely depending on what medication I'm on. Sometimes I feel pretty terrible."*** ***"Being diagnosed with myeloma has impacted me on a psychological and emotional level. It makes you kind of anxious and cautious in terms of things like the choir that I sing in. Because the choir is one of the best places available really to pick up a bug. I actually stopped going to choir before the lockdown because I just thought I can't sit here worrying about this."*** ***"I get very tired, I suffer from fatigue and secondly I'm very vulnerable to infections, so I try to avoid going to anywhere that is a crowded indoor space."*** ***"I am cross that I have to nap constantly and that having a day out means careful planning."*** ***"The main constraints are the fatigue, which is really pronounced, and breathlessness. The feeling of breathlessness isn't like when you a run a little bit. That feeling of breathlessness is like your breathing is a little bit out of control. You can get your breath back very quickly, but for me it's not like that, it's almost like you've been winded."*** In a survey of 1324 patients and carers, 72% of respondents reported that their myeloma had a high or moderate impact on their quality of life.[1]

[1] Myeloma UK (2022) A Life Worth Living The impact of a delayed diagnosis on myeloma patients' quality of life. Available at https://www.myeloma.org.uk/library/a-life-worth-living/ (Accessed September 2023)

	"***Myeloma has totally turned life upside down. Initially we felt that if we got through 6 months of treatment and the stem cell transplant everything would be ok. That hasn't been the case. The reality is that for me treatment has been constant and invasive and this is difficult, both physically and emotionally."*** ***"It has almost impossible to plan for a future. Uncertainty means that on at least 3 occasions in the last 6 years I have been seriously ill, usually with pneumonia and death has seemed imminent."*** ***"I gave up these responsibilities immediately I was diagnosed, so it brought a lot of my public duty work to a halt. By stopping doing all the activities, there was obviously a lot less to do. I find it very frustrating that I can't do things that I used to do, and influence things I used to influence.."*** It is an incurable, relapsing and remitting cancer. The aim of treatment is to control the myeloma, slowing its progression, and reducing symptom burden. The constant possibility of relapse has a huge psychological impact on patients. ***"I am aware that my life is not equivalent to my contemporaries and feel as if I am walking around with the 'Sword of Damocles' hanging over me all the time."*** ***"The difficult thing with myeloma is living with knowing that, at some point, that it's probably going to break through and you're probably going to be back to square one. There's no cure so far."*** ***"One of the key things I find is that you do get quite nervous as you wait for your light chain results every month… that is actually quite stressful, waiting for the results and sometimes they do take time to get through."*** Relapse completely disrupts the lives of patients and their families. Symptoms increase (e.g., pain, fatigue). Hospital visits and tests increase. They must switch treatments and adjust to different side effects and new routines for hospital visits/treatment administration. They also face the uncertainty of whether the new treatment will be effective and tolerable. They are aware that every time they need to change treatment, their options and life expectancy decrease. Therefore, the anxiety of relapse increases with each subsequent line ***"…by the summer I'd relapsed. It then wasn't clear what we were going to do next. That was probably the worst time, even worse than initially being diagnosed. Because it was like everything was much worse. It's like you've relapsed really quickly, its more aggressive, your prognosis is not so good"***

	The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. ***"Its just as time has gone on with nothing working for me I just feel sometimes… in despair. That you sort of think why me, why did it have to be me, and why doesn't it work like it does for others… I do worry about the future. Do I have a future?"*** ***"After 7 years, after the 1st line treatment… its been a constant blur of one treatment to another…of injections and then infusions and going to hospital"*** How well patient responds to or tolerates a drug impacts future treatment options. Myeloma also evolves and becomes resistant to treatment. In general, a drug that did not work, stops working or caused serious side effects would not be offered again, even when administered in a different combination. Therefore, it is essential to have a range of treatments with different mechanisms of action at all stages of the myeloma pathway to ensure patients have a treatment available when they need it. ***"So that's a massive reassurance to know that when I relapse from this there is something else I can go on. I haven't run out of options… because there's been points in my treatment history when it's been questionable about what options I've got left to me because there hasn't been any obvious treatment options."*** Relapsed patients, the population covered in this appraisal, often experience a more significant disease burden due to the progressive nature of the disease and the cumulative effects of treatment, which can result in reduced quality of life.[2] ***"I thought at first it would be something I could handle, because it wasn't that bad. But as the years have gone by it has progressively got worse and harder to deal with. It's dominated my life. It's dominated by hospitals, I'm always having hospital visits, it's not something that I wanted, it interferes with my life such a lot."*** Treatment side effects and frequent hospital visits have a social and practical impact on patient's lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members also affect patients' sense of control. ***"One of the most important things I want from a treatment is to not have any side effects that are really impacting on my life and being able to live a normal life as much as possible. So, less time in hospital being hooked up to anything."***

	Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[3] They are affected in many ways because of both caring and dealing with the day-to-day implications of myeloma. Many in this situation mention changes in their social life, relationships, income, and wider family dynamics. ***"In terms of the impact of having myeloma, its pretty tough on my wife. She's 15 years younger than I am. Its very tough on her. I did see my consultant in May/June last year (2024) and she said we should be thinking in terms of months not years, which for her is quite difficult."*** ***"My wife is a massive worrier, so I don't tell her a lot. She knows I'm ill. But I don't tell her half of the things that go on. Only because, she worries enough as it is."*** ***"The relationship with my partner has meant a need to adapt – from wife to carer."***

[2] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16:1 P.427
[3] Myeloma UK (2012) A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK. Available at https://www.myeloma.org.uk/documents/a-life-in-limbo/ (Accessed September 2023

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel fortunate that although myeloma is incurable, it is treatable in most cases. However, patients and carers, especially those who have already experienced relapse, are acutely aware that the range of treatment options and the chance of deep responses with long remissions decreases every time they relapse. They know about treatment resistance and that an effective treatment will stop working at some point. They also know that the range of treatment options available at the fourth line and beyond is markedly narrower than those available at first or second line. However, there is hope that newer immunotherapies like talquetamab could reverse this trend delivering good responses and long remission times at later lines. ***"I just think the more treatments we can get, that's what we need, we want to move to it (myeloma) being this manageable illness. We know it's not curable, but we want it to be manageable and treatable and get these longer periods."*** Patients want effective, appropriate treatment options at each line of their treatment. They are concerned about options becoming limited because they are resistant or intolerant to certain regimens or drugs. Patients want their haematologist to have several options available to them so they can treat their myeloma when they relapse. This includes having access to new treatments, including those with new modes of actions which demonstrate good safety and efficacy and provide as long a remission time as possible with the best quality of life. ***"In the NHS you are restricted and told this is only available at this point or you can't have this if you've had that, or haven't previously had that. Theres no logic in it, it just doesn't make sense a lot of the time. We just need to trust the medical teams a bit more. Patients want choice and want their clinicians to have the freedom to offer you the right treatment and not be restricted."*** Multiply relapsed patients also know that every myeloma patient is different. They know every patient's experience of a treatment is different and sometimes unpredictable. They know that the level of effectiveness or side effects can differ, either from direct experience of treatments not working or causing unbearable side effects or through discussions with peers. Understandably, this can cause a great deal of worry for myeloma patients and their families. There is uncertainty about the future, whether the next treatment will work and if it will negatively affect their quality of life and the fear of reaching the 'end' of treatment options for their cancer.

	"I've had many relapses, which is all so disappointing because nothing stays. I was talking to a man who had been on the same treatment for 2 years and I thought how did you manage that because I ever manage anything more than months and that's upsetting that I can't keep hold of anything. I've a feeling that this one is the final hurrah, this is probably all they've got for me…" All anti-myeloma treatments have side effects which affect quality of life. The most impactful side effects are the ones which limit daily activities or reduce independence. These include fatigue, peripheral neuropathy, and gastrointestinal disturbances.

8. Is there an unmet need for patients with this condition?	There is a clear need for innovative anti-myeloma treatments which deliver deep, durable responses for myeloma patients. There is a clear need for more effective treatments later in the pathway. Patients can be successfully retreated at relapse, but the probability of deep, durable responses decreases with every relapse. A retrospective study of patient outcomes across Europe showed that 32% of patients achieved a complete response in the first-line setting, compared with 4% at fourth line and 2% at fifth line or later. It also showed a decrease in overall response rates (ORR) with each line of treatment with 3 in 5 patients not responding to available treatments at fifth line. (ORR = 92% at first line, 84% at 2nd line, 73% at 3rd line, 64% at 4th line and 41% fifth line). [4] Patients need to have effective treatments available at each relapse. Due to the nature of myeloma, it is crucial that clinicians are always one step ahead of the cancer and that there is another treatment option 'waiting in the wings' for patients to receive, particularly where the myeloma has mutated to the point that it will not respond to currently available treatments. Patients with relapsed or refractory myeloma after four or more therapies are all too familiar with this scenario. Their disease is resistant to most existing treatments and innovative mechanisms of action are required to bring it back under control. Otherwise, the progression of the cancer is unimpeded, with serious consequences for the patients' quality of life and survival. ***"I don't know what they would give me as an alternative. I'd gone through a lot of the drugs that were available, I think I was very lucky to get it (talquetamab). I went into remission very quickly… All of my bone marrows have been negative, so I think I don't know. I think I would be dead if I hadn't got it. I think I would be struggling probably."*** More than a quarter of myeloma patients have high-risk disease at diagnosis. They either don't respond to existing treatments or relapse shortly after successful treatment. They move through the myeloma treatment pathway and run out of viable treatment options more quickly than standard-risk patients. Treatments with new mechanisms of action are a lifeline for high-risk patients with the potential to deliver significant remission times when other established classes of anti-myeloma drugs have not. ***"Unfortunately, because I have ultra-high-risk myeloma the low pill based chemotherapy wasn't effective for very long and after about a year there were signs of the cancer protein again. So, then they had to decide upon a new treatment…"*** There is a critical need to ensure that the myeloma treatment pathway offers options for each myeloma patient based on their individual health status and their response to previous treatment regimens, including tolerability and co-morbidities. Access to new myeloma treatments offer significant hope and health and wellbeing benefits, and address a major unmet

[4] Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.

	need, the need to increase duration of remission, be able to respond to relapse with a potent and long-lasting new treatment and to maintain and improve quality of life. ***"The variety of treatment I have received is evidence that the disease is complex and can be resistant to treatment. If there are options that are available that offer hope they should be available to all."*** Non-response or reduced response is caused by differences in myeloma cell biology. New drugs with innovative mechanisms of action are urgently needed to treat patients whose myeloma does not respond or has a limited response. Relapse is caused by resistance to existing treatment. Myeloma is still incurable, and even after successful treatment, almost all patients eventually become resistant to existing treatment. Treatments that have worked well at earlier lines are no longer effective. Patients with relapsed and refractory myeloma are all too familiar with this scenario. Their disease is resistant to most existing treatments, and treatments with new mechanisms of action are needed to control their myeloma. New drugs are urgently needed to overcome treatment resistance. Patients are also aware that some drugs or treatment combinations are only available at specific lines. This doesn't make sense to most patients. There is no way of knowing whether a treatment will work until you have it. There is a sometimes a feeling of having to choose between treatments or miss out on an effective treatment. ***"But I could only have that as a single agent, I couldn't have it in combination. Because the NHS pathways wouldn't allow that. Obviously, we know it works better in combination, all the consultants know it works better. But if you're not at the right point in your pathway they only give you what they are allowed, it's just so frustrating."*** ***"I think access to this treatment (talquetamab) shouldn't be one of those, where say this can only be made available at this point in the pathway i.e 5th line or 3rd line etc, it should be available, and I really feel so strongly about this, with the whole of myeloma treatments we should give so much more freedom to the medical teams i.e the consultants to say when it's appropriate to have a different thing."*** Many patients needing effective treatment at fourth line and beyond are still fit and active, particularly patients who were diagnosed when they were younger or who have quickly moved through treatment lines due to side effects or poor response rates.

	"But I'm still comparatively young and I was very healthy until I got this (myeloma). I've always enjoyed very good health with a very strong resistance to infections." Although clinical trials and compassionate use programmes may be available at later stages of the pathway, they are not accessible to all patients. Clinical trials and compassionate use programmes are often limited to a few large, specialist, inner-city hospitals. They are also only available for a finite time and to those who meet the inclusion criteria. ***'Not knowing what's going to happen in the future is difficult. There aren't any next steps and that's very difficult'***

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our research that patients value treatments which control their myeloma, keep them in remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life.[5] The MonumenTAL-1 trial showed that talquetamab offers patients these benefits. Weekly dose: In the trial, the overall response rate was 74% for the weekly dose. 34% of patients achieved a complete response or better, 59% achieved a very good partial response (VGPR) or better. The average time to response was 1.2 months and the average length of response was 9.5 months. Fortnightly dose: In the trial, the overall response rate of talquetamab was 71% for the fortnightly dose. For the fortnightly dose 39% of patients achieved a complete response or better, and 61% achieved a very good partial response (VGPR) or better. The average time to response was 1.3 months and the average length of response was 9 months. The trial is still ongoing, and it is still too early to tell what the average length of response is. however the trial results show that after 9 months that 76% of patients who got talquetamab were still responding to treatment. Talquetamab targets and kills myeloma cells in a different way compared to currently approved treatments. If approved, it could be the first NHS-commissioned T-cell engager targeting the GPRC5D protein. This addresses the need for new drugs with new mechanisms of action to combat treatment resistance. ***"I think its important we have access to new treatments, as we've gone through so many different lines for treatment. Its good that scientists are trying to find something that works in a different way"*** ***"I think it's important that these new drugs that come along have less of an interference effect if they are going to be administered. My view is this new drug (talquetamab) was a tremendous improvement from the previous ones"*** Multiply relapsed and refractory myeloma patients are especially dependent on the roll-out of innovative medicines and welcome the opportunity to access treatments which have the potential to improve their chances of survival and quality of life***.*** We spoke with patients who described talquetamab as offering hope when all other options had been exhausted. The significant impact of this on patients' quality of life and survival cannot be understated.

[5] Postmus, D., et. al. (2018). Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma. The oncologist, 23(1), 44–51.

	"It brought me back from end of life care. I was given about 6 months in Jan 2024 and I am still here. Between Jan and April 2024 when I received no treatment I was in pain and had radiotherapy on my spine, ribs, hip, shoulder , arm and neck. My myeloma has always manifested itself by bone damage and pain. For us talquetamab has been a life saver." ***"When I first got it, I was very pessimistic, I thought I'd die very soon but here I am 3 and a half years later and part of that is definitely due to the Talquetamab so I'm very grateful for it."*** The patients also expressed how quick and easy the process of receiving the treatment was and that they suffered no ill effects directly after treatment was administered. ***"Its great, you have the injection, you get out the hospital, you just carry on and you don't even think about it. It's great, it's about a 10 second injection, to have it administered is very quick. Whereas there have been other drugs like daratumumab, when that first came out that was a 90 minute to a 2 hour infusion."*** ***"After I'd had the talquetamab injections, I travelled home and I was able to carry on straight away with normal life. I had no ill effects whatsoever"*** ***"One positive thing with Talquetamab is on the day I have treatment it's all very quick and I don't notice any side effects on the day. With some of the other ones you feel a bit woozy that afternoon and I maybe would have a lie down when I get home. With this I notice nothing."*** The patients we interviewed also liked that the treatment either did not include or had limited time periods of dexamethasone. The ability to access a novel treatment without steroids that can deliver effective remissions cannot be underestimated. ***"If talquetamab allows people to come off dexamethasone I would say it's a hugely good thing because everybody hates dexamethasone. I don't think doctors realise how destructive it is for your life."*** ***"other things I've had have pretty much come with steroids. Probably everything I've had steroids with. I really hate steroids because they disrupt my sleeping. I can't sleep and then I'm irritable and I just feel rubbish. I felt tired but also unable to sleep at the same time. Very much with other treatments I've had to think ok, I'm having treatment I've got to write off the next few days at least. Where as with talquetamab I think I'm having treatment, but it doesn't stop me doing anything, apart from the time factor of having to go to hospital."***

	Although side effects could be more severe in the early phases of treatment, the patients we spoke to who had received talquetamab felt the on-going treatment side effects were more manageable than previous treatments. They felt normal and could get back to doing the things they wanted to. Patients also described some side effects as becoming more manageable if the dose frequency was reduced. Quality of life was assessed in the MonumenTAL-1 trial[6], where results showed meaningful improvements from baseline myeloma symptoms, physical function, and overall health related quality of life. These favourable results in patient reported outcomes echo the sentiments expressed through our interviews with patients regarding their quality of life whilst receiving talquetamab. ***"What talquetamab does it allows me to live an existence which is close to what I had before I had myeloma diagnosed."*** ***"You've got your routine, you go into the hospital, you have your injection, and that's it. So, to me, this drug gives a better quality of life and you can do what you did pretty much prior to being diagnosed."*** ***"I would say the side effects compared to other treatments are more manageable. I now regularly walk 3 or 4 miles, probably 6 actually. I mean I am 79 so you would expect me to be a bit tired after 6 miles. But I would say my energy levels are much better and I'm not breathless like I used to be on some of the other treatments."*** ***"I like talquetamab – it's a personal view but I find it has the two components I'm looking for – effectiveness and manageable side effects."***

[6] Schinke, C. et al (2023). Symptoms, Functioning, and Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Treated with Talquetamab: Updated Patient-Reported Outcomes from the Phase 1/2 MonumenTAL-1 Study, Blood (2023) 142 (Supplement 1): 6711.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There are three factors that patients typically consider when thinking about treatments – efficacy, side effect profile and ease of administration. The order of priority varies based on personal preference.[7] As with all anti-myeloma treatments, side effects are a disadvantage. Patients value treatments with few mild side effects that stop when treatment ends. However, in practice, patients accept varying levels of toxicity in a treatment, depending on the stage of their myeloma and whether it delivers a good survival benefit. In the MonumenTAL-1 trial, cytokine release syndrome (CRS) was reported as the most common side effect. This was reported in 77% of participants receiving the weekly dose and 80% of participants receiving the dose every other week. Other significant side effects included changes in blood cell levels, weight loss, changes in the skin and nails and a change in sense of taste. Although patients perceived these side effects as a clear disadvantage, they do not believe that this takes away from its overall benefit. In general, many myeloma patients see side effects as something to be expected as part of their treatment; they are willing to accept the immediate disadvantages in a trade-off for long-term gains or manage to develop self-care strategies in cooperation with their healthcare team. ***"I would say that the skin, taste and nails issues are quite manageable, you can live with it of course you can. My taste is slowly starting to come back."*** ***"You have to change your life, but the side effects are quite manageable to live with"*** ***"They are manageable, if they keep the disease under control then its well worth putting up with it. So quite manageable, it's not a bundle of fun, but quite manageable."*** ***"Overall the side effects are fairly minimal compared to what they might be and that is really important for people"*** ***"They are not normal nails. I'm used to it – its not as big of a deal. It's a bit like anything with treatments, you think something is a really big deal when it first happens, it is a big deal. Its like when you lose your hair. To start with it's a big deal, and then you just think its not a big deal really, it's a cosmetic thing."*** ***"I did have a cytokine release syndrome episode and it was very unpleasant. But not half as unpleasant as a stem cell transplant"***

	Some patients highlighted that skin and weight loss side effects can be effectively managed through suitable support from dermatology or dietitian input. Most of the patients we interviewed felt that the side effects associated with talquetamab were more manageable than those experienced whilst receiving other treatments. There was general feeling, particularly for patients who had no further options that the benefit of increased life expectancy far outweighed any risks. ***"The most important thing is to try and stay alive and try and keep the cancer in remission and that outweighs any of the side effects, you know, having peeling nails or flimsy skin, or feeling exhausted is much better than being dead."*** ***"Besides losing my taste, I would say compared to all previous treatments the side effects are pretty good"*** ***"In comparison to the other treatments I've had, there seems to be more of them than the other treatments I've had. The side effects are manageable though"*** ***"The side effect is not a big enough deal at all for me to say I'm not having the treatment, obviously being in remission is far more important – so I live with that."*** ***"They said that because the injection may go monthly, the taste my come back. But to be perfectly honest with you it's a small price to pay."*** In the MonumenTAL-1 trial, nearly half of the patients who received talquetamab at the weekly dose developed infections and about one third of those who received the every other week dose developed infections. Patients we interviewed felt their experience of the increased risk and number of infections was a disadvantage but noted this had been managed by access to IVIG infusions. ***"The IVIG has helped in tandem with my treatment to keep my blood counts up to an acceptable level."***

[7] Fifer, S, et. al. (2020) Myeloma Patient Value Mapping: A Discrete Choice Experiment on Myeloma Treatment Preferences in the UK, Patient Preference and Adherence, 14, 1283-1293

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The patient cohort eligible for this treatment is small. There are around 1000 patients receiving fourth-line treatment and 450 receiving 5th line treatment every year. The myeloma treatment pathway is continually evolving. The treatment given to patients at each line depends on when they were diagnosed or relapsed and the treatment available via routine commissioning or clinical trials. NICE also introduced interim guidance during the pandemic. As a result, many patients at fourth line may not have followed the current approved pathway. Any recommendation should ensure clinicians have the flexibility to give the treatment when it is most beneficial to patients based on the characteristics of their disease and overall health.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We don't anticipate that a positive recommendation would impact people protected by the equality legislation differently to the wider population. As with all treatments the costs incurred by hospital visits and time off work will have a more significant impact on people with lower incomes.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear need for innovative anti-myeloma treatments which deliver deep, durable responses for relapsed and refractory myeloma patients. • Clinical trial data and insights from our patient interviews confirm that talquetamab can deliver the most important benefits to patients: Good complete response rates and remission times, improved life expectancy and quality of life. With some indicating this treatment brought them back from end of life care when all other options had been exhausted. • If approved, talquetamab could be the first NHS-commissioned T-cell engager treatment to target G protein coupled receptor class 5 member D (GPRC5D) for myeloma. Therefore, it has much potential to overcome treatment resistance and fulfil an unmet need for multiply relapsed/refractory myeloma patients. • Insights from our patient interviews clearly show that patients who received talquetamab had a positive experience and would recommend it for approval on the NHS. • Patients consider fortnightly subcutaneous injection a distinct advantage of this treatment.

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Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of this bispecific antibody
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achievement of PR or better by MM criteria In the relapsed/refractory multiple myeloma(RRMM) setting the overall response rates (ORR) was 68% for talquetamab in the MonumenTAL-1 study
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	RRMM who have prior treatment or refractory to BCMA directed therapy

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	NICE guidance for the treatment of multiple myeloma is well defined

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a number of guidelines published, An issue is that there are a large number of novel agents used alone and in combination which have now been established making it difficult for guidelines to be fully up to data
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NICE guidance well defined at present. Complicated by the fact that the standard of care is changing and patients now eligible for later lines of therapy have had different frontline and relapsed treatment dependent upon prior duration of response
9c. What impact would the technology have on the current pathway of care?	Although there are a number of bispecific antibodies (BsAb) licenced and NICE approved for MM, there is an argument to made to favour talquetamab in some clinical scenarios. The patient population included in MonumenTAL-1 tial included patients with prior exposure to anti-BCMA therapies, and this population were noted to have good responses to talquetamab in the trial. Patients with anti-BCMA therapy exposure were excluded from participation in both MajesTEC-1 and the published MagnetisMM-3 cohort, possibly due to the potential for therapy triggered deletions in *TNFRSF17*, the gene coding for BCMA. These genomic events may make BCMA targeting BsAbs including teclistamab and elranatamab ineffective. Although the efficacy of both teclistamab and elranatamab have not been reported prospectively in patients with prior exposure to anti-BCMA therapy, small retrospective datasets have suggested there can be good efficacy in this setting. Overall, it may be prudent for clinicians to favour use of talquetamab in patients with relapse following anti-BCMA BsAb therapy or CAR T-cell, pending additional datasets guiding clinicians otherwise.

	The toxicity profile for talquetamab, a GPRC5D targeting BsAb, is also distinct from that of BCMA-targeting BsAbs. Because of “on-target, off-tumor” effects, patients in the MonumenTAL-1 study were noted to have dysgeusia (63%), and skin-related (67%) or nail-related (57%) toxicities, as GPRC5D expression is measurable in affected tissue types. Although these side effects are not typically associated with morbidity and mortality, they may be associated with significant changes to patient reported quality of life, and should be discussed when considering treatment with talquetamab as opposed to teclistamab and elranatamab.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, similar as for other approved bispecific antibodies
10a. How does healthcare resource use differ between the technology and current care?	Although there are a number of bispecific antibodies licences and NICE approved for MM, there is an argument to made to favour talquetamab in some clinical scenarios where there has been previous use of anti-BCMQ therapy and particularly where resistance has occurred or BCMA expression lost
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should be delivered in speciality clinics experiences in the use of bispecific antibodies
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Bispecific antibodies are already widely used in a number of haematological and oncological conditions and there is no additional facilities, training or equipment

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	See above. Indicated where there is prior anti-BCMA directed therapies and several of these are already NICE approved,
11a. Do you expect the technology to increase length of life more than current care?	There is data to support increased responses but I have not seen nor am I aware of data demonstrating OS advantage although this may have been submitted by the manufacturer
11b. Do you expect the technology to increase health-related quality of life more than current care?	There is data supporting improved QoL within trials of the use of this agent
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Myeloma patients, particularly those who have received and/or become resistant to BCMA directed therpay

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Can be readily delivered in settings in which other bispecific antibodies are being delivered for myeloma and/or other haematological conditions. Centres should be experienced in managing CRS and other expected AEs with this agent.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Assessment of disease response to previous therapy, and routine testing to assess response to this agent
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, suitable for patinets who no longer respond to BCMA directed therapy
16a. Is the technology a 'step-change' in the management of the condition?	Yes, novel target

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, with increased use of BCMA directed therpay it is expected that more patients will become resistant to BCMA directed therapy and this will represent an increasing unmet medical need
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	These have to be weighed against the demonstrated benefits as seen in clinical trial data

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, although CART no yet NICE approved in MM and this population very rare in the UK clinical practice
18a. If not, how could the results be extrapolated to the UK setting?	Other patients in trial setting can be assessed
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	ORR, duration of response and QoL were assessed in the trials
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Uually. Still premature to see OS data

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 1023 [TA1023]?	No
21. How do data on real-world experience compare with the trial data?	Experience has been as expected

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	There is an increased incidence of MM and particularly higher risk disease in Afro and Afro Caribbean patients and these higher risk patients are more likely to require further lines of therapy as high risk disease associated with increased risk of relapsed with prior lines of therapy
22b. Consider whether these issues are different from issues with current care and why.	See 22 a

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Talquetamab is a GPRC5D targeting bispecific antibody (BsAb) licensed for treatment of multiple myeloma • The target of talqetamab is distinct from that of BCMA-targeting BsAb • Patients with prior exposure to BCMA directed therapy and those who are resistant are most likely candidates for GPRC5D directed therapy • The side effect of talquetamab is unique in some aspects but requires no additional resources over the requirements for delivering other BsAbs

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Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 4 July 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating relapsed or refractory multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Neil Rabin
2. Name of organisation	University College London Hospitals and North Middlesex University Hospital (I am also an Executive Member of the UK Myeloma Society). I have been nominated by J and J for this appraisal.
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma? ☐ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for relapsed or refractory multiple myeloma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Multiple myeloma is incurable so the aims of treatment are 1) to prolong survival (OS) 2) to prolong time until disease progression (Progression free survival - PFS) 3) to maintain / improve quality of life (i.e part of QALY)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in PFS and/or OS whilst maintaining quality of life.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma?	Yes, as the disease is incurable and life limiting. Any treatment that prolongs time to disease progression and/or survival with acceptable side effects will help alleviate this unmet need. These patients require novel therapies with different disease targets and/or mechanisms of action.
11. How is relapsed or refractory multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Talquetamab will be given at 4th line and beyond in patients how have received a proteosome inhibitor (PI), immunomulatory drug (IMID) and anti-CD38 monoclonal antibody . Therefore the current available choices at 4th line and beyond are: 1. Teclistamab or Elranatamab (on the CDF) if the patient has received a PI, IMID and anti-CD38 monoclonal antibody. Available at 4th line and beyond. 2. Pomalidomide if the patient has received a PI/IMID/alkylator therapy (anti-CD38 monoclonal antibody not specified). Available at 4th line and beyond. Daratumumab monotherapy is not an appropriate comparator as this assumes the patient is likely to be anti-CD38 monoclonal antibody naïve and would not fulfil criteria for Talquetamab.

	Isatuximab Pomaldiomide Dexamethasone (on CDF), is not an appropriate comparator as this assumes the patient is likely to be anti-CD38 monoclonal antibody naïve and would not fulfil criteria for Talquetamab . Panobinostat bortezomib dexamethasone is not used in routine clinical practice at 4th and beyond.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Clinical teams involved in the care of patients with relapsed or refractory myeloma have already incorporated bi-specific antibodies in to NHS clinical practice. This technology will be delivered in the same way as other bispecific antibodies. The infrastructure to provide this technology is generally in place with pathways and protocols regarding safe delivery of care. This technology is administered in a secondary care setting, usually requiring inpatient stay for initial step up doses to monitor for and manage CRS. However numerous centres are using ambulatory models for this. No new investments in services are needed.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. Data from MonumenTAL-1 trial provides a clinically meaningful added benefit to relapsed myeloma patients over current care. Talquetamab offers a new therapy with a novel mechanism of action (GPRC5D × CD3 bispecific antibody) that is approved for relapsed or refractory multiple myeloma in patients how have had at 3 prior lines of therapy that includes a PI/IMID and anti-CD38 monoclonal antibody. Results from the MonumenTAL-1 phase 1/2 study demonstrate high overall response rates (around 70%) in heavily pretreated patients with relapsed or refractory multiple myeloma, including in those patients with previous T cell therapies. Side effects include CRS, dysgeusia, nail changes and weight loss are manageable. PFS is 11.2 months in the 0.8mg/kg (fortnightly group). (Chari et al, Lancet Haematology, Vol 12 April 2025).

	I would expect this therapy will be an additional treatment option for patients, with the potential to increase the length of life. Teclistamab and Pomalidomide could be offered to patients after they receive Talquetamab.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Talquetamab was shown to be effective across all subgroups. The overall response rate was consistent across triple class exposed patients and penta-class exposed patients. In particular we observed similar progression free survival irrespective of cytogenetic risk profile, this is uncommon in most myeloma trials Benefit with the biweekly dosing was also observed in patients aged 75years and over.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Those involved in the care of patients with relapsed or refractory myeloma are now well versed in the management of the toxicities of bi-specific antibodies. The management of CRS, ICANs and infection are part of standard practice. Talquetamab will be administered as a subcutaneous injection every 2 weeks. Note other available bi-specific antibodies are weekly for at least 24 weeks. The bi-weekly scheduled may allow for less impact on service delivery. Many patients on bi-specific antibodies require replacement immunoglobulin either IV or sub-cutaneous. Less severe grade 3-4 infections were observed relative to other bi-speciifc antibodies (26% Talquetamab vs 55% Teclistamab). This would potentially lead to less use of ivig. The are off target side effects including dysgeusia, weight loss and skin and nail toxicities. These are unique to the novel mechanism of action of Talquetamab and will require clinical review.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be initiated at relapse and stopped at disease progression. Other reasons for stopping include intolerance or patient decision.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	No

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Talquetamab is a first in class GPRC5D targeting bi-specific antibody that has demonstrated strong clinical efficacy in a heavily myeloma patients with relapsed myeloma (see answer to question 13). Myeloma remains incurable. This therapy provides an additional treatment option for patients that are triple class exposed/refractory, to current therapies such as Teclistamab/Elranatamab or Pomalidomide.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of CRS and ICAN are generally grade 1 and managed with established protocols already in place with other bi-specific agents. This does not impact on QoL. The side effects of dysgeusia, weight change or skin and nail toxicities are often low grade. Certainly skin and nail toxicities are benign, self-limiting and not painful and can be successfully managed with supportive care.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MonumenTAL-1 was a multicentred clinical trial, that appears representative of the UK myeloma population. The most important outcomes were the overall response rates, median duration of response and progression free survival were reported. The safety data was as previously reported.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA380], TA427, TA970, and TA1015?	No
23. How do data on real-world experience compare with the trial data?	Real world data is similar to that reported in the MonumenTAL-! Study. Real-World Safety and Efficacy of Talquetamab for Patients with Heavily Pretreated Relapsed-Refractory Multiple Myeloma (Shaikh et al, https://doi.org/10.1182/blood-2024-210976 In this real-world experience of the safety and efficacy of Talquetamab for relapsed refractory myeloma patients, results were comparable to that of the MonumenTAL-1 trial even though 40% of patients would not have been eligible.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	No equality issues

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

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Single Technology Appraisal

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Part 1: Treating relapsed or refractory multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sarah Lawless
2. Name of organisation	Belfast Health and Social Care Trust N. Ireland and UK Myeloma Society
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma? ☐ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for relapsed or refractory multiple myeloma?	Multiple myeloma remains an incurable malignancy.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aims of treatment for patients with relapsed or refractory disease include prolonging overall survival and prolonging the time in remission/time to next treatment all whilst aiming to maintain or improve the patient's quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	For patients with relapsed or refractory myeloma a clinically significant treatment response is one which improves progression free survival and overall survival. Based upon outcomes for triple class exposed patients a treatment that can increase PFS by more than 4 months or have an overall response rate of more than 30% is considered clinically significant.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma?	There is a substantial unmet need for patients with relapsed and refractory myeloma. These patients require novel therapies with different disease targets and/or mechanisms of action.
11. How is relapsed or refractory multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	1. Guidelines-We follow NICE guidance. There are also European (EMN/EHA) guidelines and International Myeloma Working Group consensus guidelines. 2. The pathway is very well defined based upon the current NICE approved regimens and therapies. This can be somewhat restrictive as it does not always allow for personalisation based upon genetic risk, co-morbidities or previous toxicities. As a clinician working in N.I. we follow NICE and hence similar pathway to England and Wales. Given the current pathway there is no significant variation across England, Wales or N.I. Scotland obviously have differences via SMC. 3. This technology would offer a novel target for patients with relapsed and refractory myeloma. The target is GPRC5D. No other myeloma therapy available via NICE pathway is targeting this. Note in the 4th line setting we currently have the option of teclistamab or elranatamab, both BCMA targeting bi-specific antibodies. Note the recent approval of belantamab, velcade and dexamethasone (BVd) in the second line setting. Belantamab in an antibody drug conjugate but also targets BCMA. Therefore for some patients in the 4th line setting a novel target is increasingly important.

	Other regimens such as pomalidomide or velcade and panobinostat are available in the 4th line setting but have largely been replaced by teclistamab and elranatamab Note that teclistamab, elranatamab, pomalidomide and velcade with panobinostat could be used after talquetamab
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Clinical teams involved in the care of patients with relapsed or refractory myeloma have already incorporated bi-specific antibodies in to NHS clinical practice. This technology will be delivered in the same way as other bispecific antibodies. The infrastructure to provide this technology is generally in place with pathways and protocols regarding safe delivery of care. This technology is administered in a secondary care setting, usually requiring inpatient stay for initial step up doses to monitor for and manage CRS. However numerous centres are using ambulatory models for this. I do not believe any additional investment is needed to introduce this technology. Note that this technology is Q2W rather than weekly like other bi-specifics available.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Randomised controlled trials of talquetamab versus current standards of care have not been reported on. However compared to historical controls it clearly has clinical benefit in terms of progression free and overall survival. As stated above it has a novel target that no other NICE approved therapy will offer. Meaningful improvements from baseline in myeloma symptoms, physical function and overall health related quality of life have been reported from the monumenTAL-1 study.

	Unlike the majority of other therapies in used in myeloma talquetamab does not involve regular dexamethasone which is often associated with significant side effects and impact in quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Talquetamab was shown to be effective across all subgroups. The overall response rate was consistent across triple class exposed patients and penta class exposed patients. In particular we observed similar progression free survival irrespective of cytogenetic risk profile, this is uncommon in most myeloma trials Benefit with the biweekly dosing was also observed in patients aged 75years and over. The ORR was lower in patients with extramedullary disease. Nonetheless the ORR was 40% for the biweekly dosing which is still clinically meaningful for this challenging group of patients
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Those involved in the care of patients with relapsed or refractory myeloma are now well versed in the management of the toxicities of bi-specific antibodies. The management of CRS, ICANs and infection are part of standard practice. Talquetamab will be administered as a subcutaneous injection every 2 weeks. Note other available bi-specific antibodies are weekly for at least 24 weeks. The bi-weekly scheduled may allow for less impact on service delivery. Many patients on bi-specific antibodies require replacement immunoglobulin either IV or sub-cutaneous. By the mechanism of action of talquetamab less IVIg was required within the clinical trial. Less severe grade 3-4 infections were observed relative to other bi-speciifc antibodies (26% talquetamab vs 55% teclistamab) The are off target side effects including dysgeusia, weight loss and skin and nail toxicities. These are unique to the novel mechanism of action of talquetamab and will require

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be initiated at relapse and stopped at disease progression as per IMWG criteria. Other reasons for stopping include intolerance or patient decision.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Bi-specific antibodies are reshaping the treatment landscape for relapsed and refractory myeloma. Talquetamab is a first in class GPRC5D targeting bi-specific antibody that has demonstrated strong clinical efficacy in a heavily pre-treated patient population. Therefore, it is indeed a step change in the management of this condition. This technology addresses the need for further options in triple class exposed patients and potentially those already exposed to BCMA targeting therapies It will provide a novel target in the treatment pathway
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of CRS and ICAN are generally low grade and managed with established protocols already in place with other bi-specific agents. This does not impact on QoL. The side effects of dysgeusia, weight change or skin and nail toxicities are often low grade. Certainly skin and nail toxicities are benign, self limiting and not painful and can be successfully managed with supportive care
20. Do the clinical trials on the technology reflect current UK clinical practice?	MonumenTAL-1 was a multicentred clinical trial. Reviewing the demographics of the trial population I do believed this can be extrapolated to UK setting.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The most important outcomes were the overall response rates, median duration of response and progression free survival. The safety data was also an importance outcome. No additional adverse events other than what was reported in the trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA380], TA427, TA970, and TA1015?	No
23. How do data on real-world experience compare with the trial data?	The overall response rates are reassuring similar. Note real world evidence has more patients with more lines of therapy including higher proportions of patients who had autologous and even allogeneic stem cell transplantation. The real world evidence has a much higher percentage of patients who would not have been eligible for the trial. This likely accounts for the shorter PFS observed. Despite having higher proportions of difficult to treat patients the overall response rates are in keeping with the clinical trial
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No equality issues

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory multiple myeloma or caring for a patient with relapsed or refractory multiple myeloma. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 4 July 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with relapsed or refractory multiple myeloma

Table 1 About you, relapsed or refractory multiple myeloma, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with relapsed or refractory multiple myeloma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory multiple myeloma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory multiple myeloma? **If you are a carer (for someone with relapsed or refractory multiple myeloma) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for relapsed or refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of talquetamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does talquetamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of talquetamab over current treatments on the NHS please describe these. For example, are there any risks with talquetamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from talquetamab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and talquetamab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

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- Click or tap here to enter text.
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Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

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3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory multiple myeloma? **If you are a carer (for someone with relapsed or refractory multiple myeloma) please share your experience of caring for them**	I have been living with Myeloma since Jan 2017 and Talquetamab is my 6th line of treatment. Since being diagnosed with Myeloma, I have lived with constant uncertainty, not knowing if a treatment will be effective or how long it will last. I'm aware of running out of options and I have been in the situation on several occasions when there has not been an obvious pathway. Over 7 plus years of treatment, I have experienced times when I have been very unwell and had hospital admissions due to infections. Many treatment options require a period of hospital admission, and this is always a worrying situation. Being in hospital makes me very anxious and there have been times when I have not known if I am getting better. Having to be an inpatient, especially when unable to leave the ward, makes the reality of having an incurable cancer impossible to forget. After treatments such as a stem cell transplant, DT-PACE and CAR-T, I have been neutropenic and this vulnerability to infection is very scary. At these times, I have been quite isolated and not felt able to see family and friends. The worry of getting an infection that could kill me is very stressful. Many treatments include high doses of the steroid dexamethasone, which has a massive impact on my life. Disruptive sleep and total exhaustion make normal life impossible for me although I have been in this position many times. Having Myeloma means that I don't plan in years, only in months at a time. When other people talk about their future plans, I don't think that I can do that. The worry of relapsing is always in the back of my mind, especially when waiting for blood

	results. However, I do feel lucky that I am on a treatment that is working for me and my overall health is very good. I do everything I can to stay fit and healthy as I feel that this is something I can control whereas I have no control over my Myeloma. Myeloma is part of my life now; it has meant that I have taken early retirement from a job I loved due to the risks of infection. I have regular hospital visits but I try and not let this impact me too much.
7a. What do you think of the current treatments and care available for relapsed or refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatments available depend very much on which line of treatment you are currently on and what treatment's (drugs) you have previously had. It means that a treatment that may have good results and would be beneficial is not available as the guidelines dictate that it is only offered at certain lines of treatment, This is incredibly frustrating and upsetting when you are denied a treatment, or combination of drugs, that has been proven to work. Most of the Myeloma patients I know and chat to also share this frustration. We all would like our medical teams to have more freedom in offering the best treatment for us. The current treatments have improved greatly since I was first diagnosed, but there is still a lack of options for patients once we are beyond 4th line treatment. Each time you move on another line of treatment the options diminish, and the worry is that there will be no treatments left. This is a fear that most patients who have had many lines of treatment share. We all want something to work long term but also to know we have not run out of options altogether.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Many current treatments for Myeloma such as a stem cell transplant, require spending time in hospital as an inpatient for several weeks and have a long recovery time. Other treatments require regular visits to the day unit to receive treatment through IV infusion over several hours. This is very time consuming and makes continuing to be in paid employment difficult. There is also an impact on

	patient's family and friends, either taking on more of a carers role or supporting financially. The side effects of many treatments are impactful, especially sleep disruption and extreme fatigue. In addition, lots of treatment options require the patient to be taking oral medication on a daily basis, but sometimes on a complex schedule. This is difficult for some patients to keep on top off, especially if suffering from fatigue.
9a. If there are advantages of talquetamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does talquetamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	The most important advantage of Talquetamab over most other treatments I have received is that I can continue to live my life normally and that it has given me a long lasting response. The actual treatment is a quick sub-cutaneous injection which is painless and has no impact on the rest of my day. Although I have now retired, I feel that I am well enough to be at work if I chose to do so. Currently I volunteer at a gardening charity one day a week, look after my grandchildren, attend yoga classes, go to the gym and run regularly. I completed a half marathon this year as well as last, both since starting talquetamab. My energy levels on talquetamab are much better than on some previous treatments. Although my antibody levels are low, I have not needed to have IVIG treatment and have not had many infections. The impact on my life of talquetamb treatment is far less than other NHS treatments I have received.

10. If there are disadvantages of talquetamab over current treatments on the NHS please describe these. For example, are there any risks with talquetamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only disadvantage of talquetamab over a few other treatments currently available is the need to receive treatment in the day unit. In the future I believe there may become an option of self administering talquetamab at home which would be even better. There are different side-effects with talquetamab than with other treatments I have received – loss of taste and nail problems. Although the loss of taste was initially quite difficult and I had associated weight loss, this is not an unmanageable side effect. The risks associated with talquetamab are similar to other treatment options and this may be of concern to some people.
11. Are there any groups of patients who might benefit more from talquetamab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who are unable to have other treatments, such as ASCT or who have already been exposed to BCMA targeted therapies would benefit from talquetamab. I can't think of any particular group that would benefit less.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and talquetamab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Not that I can think of.

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13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Talquetamab is an effective treatment and a good option for patients who have had several lines of treatment already.
- The side effects are very manageable.
- The treatment is quick and pain free.
- This treatment allows patients to have a good quality of life.
- My experience of talquetamab has been positive.

Thank you for your time.

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External Assessment Group

Title: *ID5082 Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies*

Produced by	*Birmingham Centre for Evidence and Implementation Science (formerly Warwick Evidence)*
Authors	*Aziza Osman Centre for Evidence and Implementation Science University of Birmingham* *Dr Adel Elfeky Centre for Evidence and Implementation Science University of Birmingham* *Dr Martin Connock, Centre for Evidence and Implementation Science University of Birmingham* *Dr Peter Auguste, Centre for Evidence and Implementation Science, University of Birmingham* *Dr Alex Tsertsvadze, Independent Consultant* *Mubarak Patel, Centre for Evidence and Implementation Science University of Birmingham* *Anna Brown, Centre for Evidence and Implementation Science University of Birmingham* *Prof Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy* *Prof Amy Grove, Centre for Evidence and Implementation Science University of Birmingham*
Correspondence to	*Prof Amy Grove* *Centre for Evidence and Implementation Science* *Park House* *University of Birmingham* *Birmingham, B15 2TT*
Date completed	*29/05/2025*

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Declared competing interests of the authors
None

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Dr Hannah Victoria Giles, Consultant Haematologist with a specialist interest in plasma cell disorders, University Hospital Birmingham NHS Foundation Trust.
Professor Aileen Clarke, Medical Director, CEIS, University of Birmingham.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Dr Martin Connock critiqued the company survival analysis and conducted EAG additional analysis. Aziza Osman critiqued the cost-effectiveness evidence. Dr Peter Auguste and Prof Xavier Armoiry provided senior oversight of the cost-effectiveness analysis. Dr Alex Tsertvadze led the critique of the clinical effectiveness evidence with Dr Adel Elfeky, and Mubarak Patel provided statistical oversite. Anna Brown critiqued and updated the company SLR searches. Professor Amy Grove led the project.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue.

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Abbreviations

Acronym	Definition
ADC	Antibody-drug conjugate
AE	Adverse effects
AESI	Adverse event of special interest
AF	Acceleration Factor
AFT	Accelerated Failure Time
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
ATC	Average effect of treatment in control group
ATE	Average treatment effect
ATO	Average treatment effect on the overlap population
ATT	Average treatment effect for the treated
BCMA	B cell maturation antigen
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BsAb	Bispecific antibodies
CAR-T	Chimeric antigen receptor-T cell
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CQ	Clarification Question
CR	Complete response
CRS	Cytokine release syndrome
CS	Company Submission
CSR	Clinical study report
DCO	Data cut-off
DLT	Dose limiting toxicity
DoR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMD	Extramedullary plasmacytoma
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire
EQ-5D	EuroQol Five Dimensions Five Level Questionnaire
GPRC5D	G protein-coupled receptor class 5D
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Appraisal
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost effectiveness ratio

ICU	Intensive care unit
IgG	Immunoglobulin-G
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
INHB	Incremental net health benefit.
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IRC	Independent review committee
IsaPomDex	Isatuximab with pomalidomide and dexamethasone
ISS	International Staging System
ITC	Indirect treatment comparison
IV	Intravenous
IxaLenDex	Ixazomib plus lenalidomide plus dexamethasone
IVIg	intravenous immunoglobulin
KM	Kaplan-Meier
L	Line of Treatment
LDH	Lactate dehydrogenase
LOT	Line of treatment
LYG	Life years gained
MA	Marketing Authorisation
mAb	Monoclonal antibody
MAIC	Matched Adjusted Indirect Comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly index of medical specialities
MM	Multiple myeloma
mos	months
MRD	Minimal residual disease
NA	Not applicable
NCT	National Clinical Trial
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PanBorDex	Panobinostat plus bortezomib and dexamethasone
PAR	Public assessment report
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PGI-S	Patient Global Impression of Severity
PH	Proportional hazard
PI	Proteasome inhibitor
PICO	Patient, intervention, comparison, outcome

PomDex	Pomalidomide plus dexamethasone
PP	Post-progression
PPS	Post-progression survival
PRO	Patient reported outcome
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses
PS	Propensity score
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
Q2W	Biweekly
QW	Weekly
ROBINS-I	Risk of Bias In Non-randomized Studies
RP2PD	Recommended phase 2 dose
RR	Relative risk
RRMM	Relapsed or refractory multiple myeloma
RWE	Real-world evidence
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SE	Standard error
SelDex	Selinexor plus dexamethasone
SLR	Systematic literature review
SMD	Standardised mean differences
SmPC	Summary of product characteristics
SoC	Standard of care
SS	Statistically significant
STA	Single Technology Appraisal
TA	Technology appraisal
TAL	Talquetamab
TCE	Triple-class exposed
TCR	T-cell receptor
TEAE	Treatment emergent adverse event
TEC	Teclistamab
TSD	Technical support document
TSE	Two-stage estimation
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTR	Time to response
VGPR	Very good partial response
WTP	Willingness-to-pay

Executive Summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section **Error! Reference source not found.** provides an overview of the key issues. Section 0 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0 to **Error! Reference source not found.** explain the key issues in more detail.

Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report. All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

Table 1 presents a summary of the key issues identified in this appraisal of the clinical and cost-effectiveness of talquetamab within its full marketing authorisation for patients with relapsed or refractory multiple myeloma (RRMM) who have had at least three prior therapies, and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb), and whose disease has progressed on the last therapy.

Table 1: Summary of EAG key issues

ID5082	Summary of issue	Report sections
Issue 1: Limited clinical effectiveness data	There is no head-to-head clinical trial evidence to capture the pure effects and costs of Talquetamab against Teclistamab.	Table 7: Summary of decision problem Section 2.1.3 and Section 2.2.1
Issue 2: Generalisability of key trials to NHS practice	Limited generalisability of key trial to NHS practice. There were no UK patients in the trial evidence for the intervention (Talquetamab via MonumenTAL-1).	Section 2.2.1.1 Section 2.2.1.3
Issue 3: Company's indirect treatment comparison hazard ratio for overall survival	The EAG has reservations regarding the reliability of the ITC OS hazard ratio. The EAG investigated a range of alternative HRs to the ITC value ([redacted]) so as to gauge the impact of HR for OS upon the company's economic analysis results.	Section 2.2.7, Section 2.2.7.1, and Section 3.4.6
Issue 4: Calibrated lognormal modelling of OS, PFS and TTD teclistamab	The company's choice of and use of calibrated lognormal modelling of OS, PFS and TTD teclistamab. The EAG undertook analyses to explore the impact of changing the modelling of teclistamab OS, PFS and TTD, separately while applying the proportional hazards derived by the company to model talquetamab OS, PFS and TTD. Using uncalibrated Weibull modelling of teclistamab OS, PFS and TTD resulted in ICERs of £32,437, £28,912 and £25,672, respectively.	Section 3.4.6

Issue 5: Intravenous immunoglobulin use not captured appropriately in the model	The company economic model assumes greater use of IVIg use in the teclistamab arm than in the talquetamab arm. The costs deriving are therefore greater in the teclistamab arm than the talquetamab arm. In scenario analysis, the EAG assumes equal use of IVIg in both talquetamab and teclistamab.	Section 2.2.6, Section 3.4.10, Section 3.4.10.3.1
Issue 6: Inclusion of subsequent talquetamab treatment	The company excluded subsequent treatment with talquetamab following teclistamab treatment. The EAG identified this as important to allow for a fair comparison of the competing interventions. Inclusion of the subsequent talquetamab treatment increased the company's base-case ICER by [redacted]%.	Section 2.2.2.5, Section 3.4.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are in the selection of survival analysis distributions, the discounting included in the economic model and the impact of subsequent treatments on the results. The EAG conducted exploratory analysis regarding the overall survival hazard ratio to demonstrate uncertainty in the results of the company's indirect treatment comparison.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- By changing the overall survival (OS)
- By changing the progression-free survival (PFS)

Overall, the technology is modelled to affect costs by:

- Drug acquisition, drug administration, and subsequent treatment costs

- Health state management costs
- Adverse event costs and end-of-life care costs.

The modelling assumptions in the EAG model that have the greatest effect on the ICER are:

- Talquetamab versus teclistamab OS hazard ratio (HR)
- Talquetamab versus teclistamab time-to-treatment discontinuation (TTD)
- Equal use of intravenous immunoglobulin (IVIg) treatment between both arms. i.e., assumed that [redacted]% of people in the teclistamab cohort start IVIg treatment

1.3. The decision problem: summary of the EAG's key issues

Report section	Table 7: Summary of decision problem Section 2.1.3 and Section 2.2.1 EAG additional analysis Sections 2.2.7.1 and 3.4.6
Description of issue and why the EAG has identified it as important	There is no head-to-head clinical trial evidence to capture the pure effects and costs of talquetamab against teclistamab. Submitted evidence for talquetamab and teclistamab came from two single arm studies; MonumenTAL-1 and MajesTEC-1.
What alternative approach has the EAG suggested?	None. The EAG performed extensive exploratory analysis to demonstrate the uncertainty in the results presented in the CS clinical effectiveness evidence. However, model inputs for clinical effectiveness remain unchanged.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers no such clinical evidence is available to resolve uncertainty.

	Further independent clinical opinion on the relative effectiveness of talquetamab versus teclistamab may inform committee decision making.

The EAG's key issue related to the decision problem are listed in the Issue 1 Table below.

Issue 1: Limited clinical effectiveness data

The clinical effectiveness evidence: summary of the EAG's key issues

The EAG's key issue related to the clinical effectiveness evidence are listed in the Issue 2 Table below.

Issue 2: Generalisability of key trials to NHS practice

Report section	Section 2.2.1.1 Section 2.2.1.3 EAG additional analysis Sections 2.2.7.1
Description of issue and why the EAG has identified it as important	Limited generalisability of key trials to NHS practice. There were no UK patients in the trial evidence for the intervention (Talquetamab, MonumenTAL-1). A total of [redacted] patients were enrolled in comparator trial (Teclistamab, MajesTEC-1).
What alternative approach has the EAG suggested?	None In the absence of UK data in NHS settings, the EAG performed exploratory analysis using real world studies in European settings to demonstrate the potential impact of talquetamab in routine clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers no such clinical evidence is available to resolve uncertainty. Further independent clinical opinion on the generalisability of participants enrolled into MonumenTAL-1 and MajesTEC-1 may inform committee decision making.

Issue 3: Company's indirect treatment comparison (ITC) hazard ratio for overall survival

Report section	Section 2.2.7, Section 2.2.7.1, and Section 3.4.6
Description of issue and why the EAG has identified it as important	The company conducted an ITC to determine the overall survival hazard ratio for talquetamab versus teclistamab. The value applied in modelling was [redacted]. The EAG has reservations regarding the reliability of the ITC HR. These are based on the following: a] The ITC appears not to have considered the impact of COVID 19 upon the survival of the unvaccinated MajesTEC-1 population. This could result in an underestimate of teclistamab survival and a HR more favourable to talquetamab than warranted. b] Regression studies of phase 3 studies indicate that the company's ITC HR of [redacted] (based on two different single arm studies) is an outlier and is over favourable to talquetamab. c] Recently published real-world studies from Europe suggest that the company's ITC dependent modelling of talquetamab survival is over optimistic while the modelling of teclistamab is over pessimistic. This suggests there will be bias that favours talquetamab over teclistamab in the company's economic analysis
What alternative approach has the EAG suggested?	The EAG investigated a range of alternative HRs to the ITC value ([redacted]) so as to gauge the impact of HR for OS upon the company's economic analysis results.
What is the expected effect on the cost-effectiveness estimates?	Increasing the hazard ratio upwards, guided by the published regression analyses, suggest increasing values for the ICER.

What additional evidence or analyses might help to resolve this key issue?	Scenarios could be conducted based upon the recent real world European studies (France and Germany) of talquetamab and teclistamab. EAG additional analysis demonstrate that OS for talquetamab compared to teclistamab from the CS ITC is an outlier compared to these real-world studies. Such analyses may be more relevant to the UK than the results from MajesTEC-1 and MonumenTAL-1 studies. The MonumenTAL-1 trial did not include any patients from the UK, only [redacted] patients from the UK were enrolled in MajesTEC-1.

Issue 4:Calibrated lognormal modelling of OS, PFS and TTD teclistamab

Report section	Section 3.4.6

Description of issue and why the EAG has identified it as important	The company's choice of and use of calibrated lognormal modelling of OS, PFS and TTD teclistamab. **Modelling of OS**: The company proportional hazards modelling of OS and PFS employed a lognormal model. Unadjusted lognormal models produce implausible extrapolation. To bring lognormal OS and PFS teclistamab models into a plausible range on extrapolation the models were forced to follow a pre-determined trajectory from 5 to 15 years. The resulting models were thereby opinion-led rather than evidence based. The company stated that the resultant talquetamab extrapolations after applying the ITC HRs to the calibrated ATT-weighted teclistamab extrapolations were then capped for GPM. a] The EAG has reservations regarding the reliability of the ITC OS HR, these reservations indicate that the resulting model is likely biased in favour of talquetamab and is associated with considerable uncertainty unexplored in the submission. b] The EAG do not agree that a lognormal model is the most suitable choice of parametric for a proportional hazards approach. Other more appropriate models should be explored. **Modelling of PFS**: Likewise, teclistamab PFS beyond the trial period was modelled using a calibrated lognormal curve and was opinion-led rather than evidence based. **Modelling of TTD**: The same approach was used to model TTD. The unadjusted lognormal model predicts that people would remain on treatment beyond 20 years and some beyond 30 years, which EAG consider to be implausible.

What alternative approach has the EAG suggested?	The EAG considers the uncalibrated Weibull model a more suitable choice for modelling OS, PFS and TTD for teclistamab and talquetamab. First, it fits closely with the clinical predictions whereas the lognormal model is forced to comply with opinion-based calibration. Second, the EAG opinion is that the Weibull model is better suited to a proportion hazards approach than the lognormal AFT model.
What is the expected effect on the cost-effectiveness estimates?	The EAG undertook analyses to explore the impact of changing the modelling of teclistamab OS, PFS and TTD, separately while applying the proportional hazards derived by the company to model talquetamab OS, PFS and TTD. Using uncalibrated Weibull modelling of teclistamab OS, PFS and TTD resulted in ICERs of £32,437, £28,912 and £25,672, respectively.
What additional evidence or analyses might help to resolve this key issue?	To fully capture the impact of using calibrated lognormal modelling of OS, PFS and TTD compared to uncalibrated Weibull modelling, would require re-analysis of the ITC HRs. See Section 3.4.6 with our concerns relating to the ITC HRs.

The cost-effectiveness evidence: summary of the EAG's key issues

The EAG's key issue related to the clinical effectiveness evidence are listed in the Issue 5 Table below.

Issue 5:Intravenous immunoglobulin use not captured appropriately in the model

Report section	Section 2.2.6, Section 3.4.10, Section 3.4.10.3.1
Description of issue and why the EAG has identified it as important	The company economic model assumes greater use of IVIg use in the teclistamab arm than in the talquetamab arm. The costs deriving are therefore greater in the teclistamab arm than the talquetamab arm. The EAG assume IVIg is used to mitigate effects of infection and is only received by live patients. Therefore, IVIG use will depend on infection rate and the proportion remaining alive. The EAG disagree with the company for the following reasons: a] At cut-off (after about [redacted] months) 71% of Cohort C have had an infection while at [redacted] months [redacted]% are still alive and can receive IVIg. In contrast at Majes TEC-1 cut off [redacted]% have had an infection but only [redacted]% are still alive to receive IVIg. It is evident that there will be more use of IVIg in the talquetamab arm than in the teclistamab arm over the first ~[redacted] months. b] Beyond [redacted] months there is likely to be continued use of IVIg. At 15 years, only about [redacted]% of the teclistamab arm remain alive compared with [redacted]% of talquetamab arm. It is evident that beyond 15 years IVIg usage will be greater in the talquetamab arm than the teclistamab arm, because few in the teclistamab arm are alive to receive IVIg. c] Real world studies from France and Germany suggest that prophylaxis with IVIg may be routine in practice to mitigate against infections in immune-compromised patients that would lead to interruptions in the use of effective therapies. The EAG considers this would be the likely case in UK practice. Because the submission models more patients survive in the talquetamab arm than the teclistamab arm this infers greater routine use of IVIg in the talquetamab arm.
What alternative approach has the EAG suggested?	In the absence of better evidence in scenario analysis the EAG assumes equal use of IVIg in both arms. The EAG acknowledge that this is a conservative approach that will tend to favour talquetamab in the economic analysis.

What is the expected effect on the cost-effectiveness estimates?	EAG would expect that the difference in costs between arms will change so that the ICER is somewhat increased.
What additional evidence or analyses might help to resolve this key issue?	Scenarios could be conducted in which costs allocated to the use of IVIG are related more directly to survival than in the company's base-case.

Issue 6: Inclusion of subsequent talquetamab treatment

Report section	Section 2.2.2.5, Section 3.4.3
Description of issue and why the EAG has identified it as important	The company excluded subsequent treatment with talquetamab following teclistamab treatment. The EAG identified this as important to allow for a fair comparison of the competing interventions.
What alternative approach has the EAG suggested?	The EAG included subsequent talquetamab treatment, which the company referred to as the 'all-in' approach.
What is the expected effect on the cost-effectiveness estimates?	The key driver of the economic analysis was the OS hazard ratio. However, given EAG concerns raised about the company's OS HR (see Section 3.4.5) this might have impacted the OS HR by excluding/including subsequent talquetamab/teclistamab treatment. Inclusion of the subsequent talquetamab treatment increased the company's base-case ICER by [redacted]%.
What additional evidence or analyses might help to resolve this key issue?	No further analyses.

Summary of EAG's preferred assumptions and resulting ICER

The EAG made changes to the company's base-case model, which formed the EAG's base-case model. The impact of each of these changes to the company's model is presented in Table 2.

The EAG's preferred assumptions include:

- Uncalibrated Weibull modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS.
- Uncalibrated Weibull modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS.
- Uncalibrated Weibull modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD.
- Exclude half-cycle correction.
- Discounting from Year 1 onwards.
- We assumed that the people who received subsequent talquetamab and teclistamab treatment would require intravenous immunoglobulin (IVIg) treatment. In the absence of data, we assumed that [redacted] of people who received subsequent talquetamab treatment would require IVIg treatment and [redacted] of people who received subsequent teclistamab treatment would require IVIg treatment.
- Include subsequent talquetamab treatment for a fair comparison of the competing interventions.
- Exclude of AE disutilities.

The EAG preferred assumptions do change the ICER as shown in Table 2 and should be viewed as partially addressing/exploring issues in the company analysis.

No modelling errors were identified or corrected by the EAG (see Section **Error! Reference source not found.**).

Table 2: Summary of EAG's preferred assumptions and ICER

EAG's preferred assumption		Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)	Impact to the company's base-case ICER
Company's base-case		[redacted]	[redacted]	£29,277	[redacted]
1.	Uncalibrated Weibull modelling of teclistamab OS	[redacted]	[redacted]	£32,437	[redacted]
2.	Uncalibrated Weibull modelling of teclistamab PFS	[redacted]	[redacted]	£28,912	[redacted]
3.	Uncalibrated Weibull modelling of teclistamab TTD	[redacted]	[redacted]	£25,672	[redacted]
4.	No half-cycle correction	[redacted]	[redacted]	£29,492	[redacted]
5.	No discounting in the first year	[redacted]	[redacted]	£29,286	[redacted]
6.	Additional IVIg treatment – talquetamab (6 doses) and teclistamab (9 doses)	[redacted]	[redacted]	£30,157	[redacted]
7.	Inclusion of subsequent talquetamab treatment	[redacted]	[redacted]	£29,109	[redacted]
8.	Exclude AE disutilities	[redacted]	[redacted]	£29,421	[redacted]

AE, adverse events, ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

EAG deterministic results

In Table 3, we present the EAG deterministic results based on the EAG's preferred assumptions.

Table 3: EAG's deterministic base-case results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Talquetamab	[redacted]	5.51	[redacted]	-	-	-	-
Teclistamab	[redacted]	2.66	[redacted]	[redacted]	2.85	[redacted]	£30,106

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained

EAG probabilistic sensitivity analysis results

In Table 4, we present the EAG probabilistic results based on the EAG's preferred assumptions.

Table 4: EAG's probabilistic base-case results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Talquetamab	[redacted]	5.49	[redacted]	-	-	-	-
Teclistamab	[redacted]	2.68	[redacted]	[redacted]	2.81	[redacted]	£31,083

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained

Summary of the exploratory analysis undertaken by the EAG

Further exploratory scenario analysis using the company's base-case model is presented in Table 5. For further details of the exploratory analyses conducted by the EAG see Section 3.4.5.

Table 5: EAG scenario analyses based on the company's base-case results

Scenario	Talquetamab versus teclistamab			
	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
Company base-case	[redacted]	[redacted]	£29,277	[redacted]

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
1.	Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment	[redacted]	[redacted]	£33,500	[redacted]
2.	Talquetamab vs teclistamab OS HR is 0.55	[redacted]	[redacted]	£35,075	[redacted]
3.	Talquetamab vs teclistamab OS HR is 0.60	[redacted]	[redacted]	£41,134	[redacted]
4.	Talquetamab vs teclistamab OS HR is 0.65	[redacted]	[redacted]	£48,893	[redacted]
5.	Talquetamab vs teclistamab OS HR is 0.70	[redacted]	[redacted]	£59,167	[redacted]
6.	Talquetamab vs teclistamab OS HR is 0.75	[redacted]	[redacted]	£73,425	[redacted]
7.	Talquetamab vs teclistamab OS HR is 0.80	[redacted]	[redacted]	£94,516	[redacted]
8.	Talquetamab vs teclistamab OS HR is 0.85	[redacted]	[redacted]	£128,856	[redacted]
9.	Talquetamab vs teclistamab OS HR is 0.90	[redacted]	[redacted]	£194,755	[redacted]

INHB, incremental net health benefit; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

Scenario analysis using the EAG's base-case model

Further exploratory scenario analysis using the EAG's base-case model in presented in Table 6. For further details of the exploratory analyses conducted by the EAG see Section 3.4.5.

Table 6: EAG's deterministic scenario analysis results for talquetamab versus teclistamab, using PAS prices

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
EAG's base-case		****	****	£30,106	[redacted]
1.	Equal to initial doses for people who require IVIg treatment following subsequent talquetamab and teclistamab	[redacted]	[redacted]	£30,091	[redacted]
2.	Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment	[redacted]	[redacted]	£34,129	[redacted]
3.	Exclude unit costs associated with treating infections	[redacted]	[redacted]	£30,432	[redacted]
4.	All out- removal of all non-routine UK treatment and removing teclistamab from MonumenTAL-1	[redacted]	[redacted]	£31,620	[redacted]
5.	Utility values from MajesTEC-1	[redacted]	[redacted]	£31,789	[redacted]
6.	Talquetamab OS/PFS/TTD, individually fitted	[redacted]	[redacted]	£22,256	****
7.	Talquetamab vs teclistamab OS HR is 0.55	[redacted]	[redacted]	£36,041	[redacted]
8.	Talquetamab vs teclistamab OS HR is 0.60	[redacted]	[redacted]	£42,621	[redacted]

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**	**INHB (£30,000 per QALY)**
9.	Talquetamab vs teclistamab OS HR is 0.65	[redacted]	[redacted]	£51,039	[redacted]
10.	Talquetamab vs teclistamab OS HR is 0.70	[redacted]	[redacted]	£62,174	[redacted]
11.	Talquetamab vs teclistamab OS HR is 0.75	[redacted]	[redacted]	£77,618	[redacted]
12.	Talquetamab vs teclistamab OS HR is 0.80	[redacted]	[redacted]	£100,501	[redacted]
13.	Talquetamab vs teclistamab OS HR is 0.85	[redacted]	[redacted]	£138,058	[redacted]
14.	Talquetamab vs teclistamab OS HR is 0.90	[redacted]	[redacted]	£211,196	[redacted]

INHB, incremental net health benefit; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

External Assessment Group Report

1 INTRODUCTION

This single technology appraisal (STA) was conducted to appraise the clinical and cost-effectiveness of talquetamab for treating relapsed or refractory multiple myeloma (RRMM) after three categories of therapy. The company submission (CS) is aligned with the marketing authorisation (MA) of talquetamab, which states

"for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody (mAb) and have demonstrated disease progression on their last therapy (triple-class exposed [TCE] patients)".[1]

The Medicines and Healthcare products Regulatory Agency (MHRA) for the UK gave a positive opinion on talquetamab (9th October 2023) having received a European Commission decision on 21 August 2023 in accordance with advice from the Committee for Medicinal Products for Human Use (CHMP).[2]

In this External Assessment Group (EAG) report, references to the CS are to the company's full evidence submission. Additional evidence was provided by the company during the clarification stage.

1.1 Background

1.1.1 Disease overview

Multiple myeloma (MM) is a progressive and incurable bone marrow neoplasm, caused due to abnormal proliferation of plasma cells derived from B lymphocytes.[3] In the UK, the treatment options are limited for patients who have received previously exposed to an IMiD, a PI, and an anti-CD38 mAb and who have progressed on their last therapy (referred to as Triple Class Exposed [TCE]). Typically, the clinical course of MM includes periods of treatment and remission separated by unavoidable relapses, with duration of response to treatment decreasing with subsequent lines of treatment. In advanced stages of MM, patients' health-related quality of life (HRQoL) significantly decreases with high symptom burden and multi-organ involvement.

The EAG clinical advisors confirm that the disease becomes more complex with its advancement with resistance to different classes of therapies and it is acknowledged that there is a reduction of treatment options as disease progresses. MM is more commonly diagnosed in men than in women.[4] It is more likely to be diagnosed in Black ethnic groups and is less commonly diagnosed in Asian ethnic groups when compared to White ethnic groups.[4]

1.1.2 Treatment landscape of MM

Globally, MM accounts for approximately 2% of all new cancer cases (estimated in 2017-2019).[3] In the UK, 6,200 new cases of MM are detected each year, deaths due to MM are estimated at 3,098 per year, equivalent to more than eight deaths per day in the UK.[3] Like most other malignancies, the incidence of MM increases with age. In the UK, an average of 43% of new cases are in people who are aged 75 years and above.[15] Associated comorbidities at this older age further increase disease complexity and reduce treatment efficacy.

With the introduction of newer treatments in the treatment landscape of MM (e.g., Pomalidomide plus Dexamethasone [TA427], Daratumumab [TA783]), patients' progression free survival (PFS) and overall survival (OS) have increased.[16] The 5-year and 10-year survival rates for patients in England with myeloma at all treatment lines are 55% and 30%, respectively.[4]

1.1.3 Talquetamab

Talquetamab (Talvey®) is a humanised immunoglobulin G4-proline, alanine, alanine bispecific antibody that binds to a cluster of differentiation (CD) 3 receptors expressed by T cells (hence TCR - T-cell receptor) and also to the G protein-coupled receptor class 5D (known as GPRC5D) (CS Section 1.2 provides more detail of the mechanism of action). GPRC5D is present in MM cells but is minimally present in normal immune cells. Talquetamab is therefore, designed to differentially encourage destruction of MM cells.

Talquetamab is available as a 2mg/ml and a 40mg/ml solution for subcutaneous (SC) injection and can be administered subcutaneously on a weekly (0.4 mg/kg per dose) or biweekly (every 2 weeks [0.8 mg/kg per dose]) dosing schedule (CS Section 1.2). The company's anticipated positioning of Talquetamab in the treatment pathway of MM is as depicted in Figure 1.

Having reviewed this pathway, the EAG clinical advisors stated that Elranatamab would be a reasonable comparator to include in this appraisal and reported its use in current NHS practice. However, the EAG notes that Elranatamab (TA1023) is only available to patients as part of a Managed Access Agreement.[5] Additional evidence collection for this technology is currently underway. After this, NICE will decide whether to recommend its use by the NHS and updated guidance will be made available. Therefore, Elranatamab (TA1023) is not considered further in this appraisal.

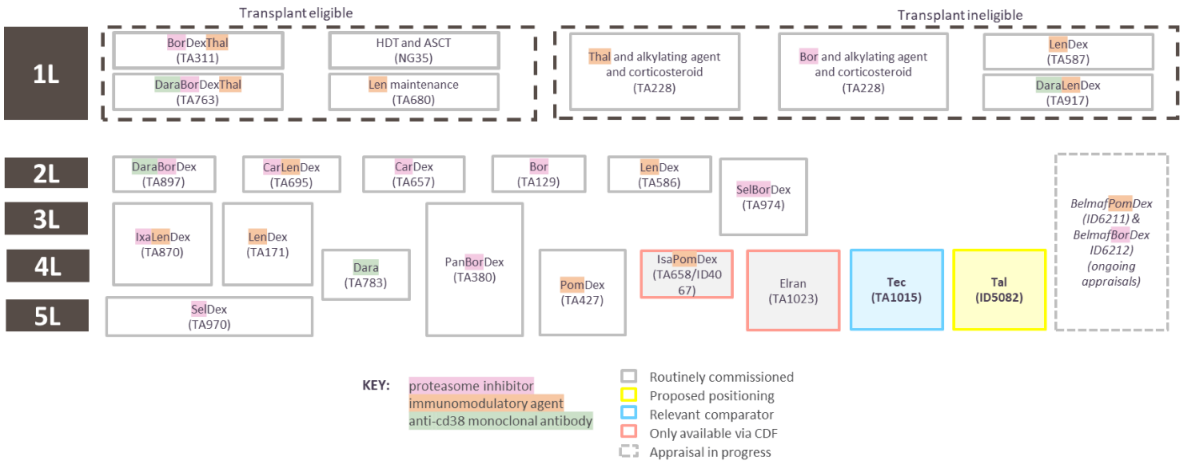

Figure 1. Current NHS MM treatment pathway and proposed positioning of talquetamab [CS Figure 4]

1.2 Critique of company's definition of decision problem

The CS decision problem partially matches the decision problem for the technology of interest, population, and outcomes as defined in the NICE's Final Scope.

There were differences in comparator and outcome definitions which were largely justified during the recent appraisal of teclistamab [TA1015].[6] TA1015 demonstrated the clinical, heath-related quality of life (HRQoL) and economic benefits of teclistamab versus the comparators included in the NICE Final Scope (see Table 7). The company states that teclistamab therefore, represents current standard of care and is the most relevant comparator to talquetamab. The EAG clinical advisors agreed that this was an appropriate assumption, and the EAG accept teclistamab [TA1015] as the most relevant comparator for this appraisal.

The Company included one additional outcome *Minimal residual disease (MRD) negativity rate.* The EAG asked for further clarification on the addition of this outcome which was provided during clarification response (CQ A.1 "*MRD-negativity rate was added to the list of outcomes in the submission as it was measured in the MonumenTAL-1 trial*"). The EAG clinical advisor noted that MRD can be assessed in the UK and is "*probably a superior measure of response*", however, MRD is "*not available in many UK centres*" and is not standard part of routine practice, (i.e., only used in trial settings.)

See Table 7 for further explanation.

Table 7: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment
Population	Adults with relapsed or refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. If the evidence allows, the following subgroups will be considered: • Prior T-cell redirection therapy • Prior lines of therapy	Adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	*Evidence provided in the recent NICE appraisal of teclistamab demonstrated that teclistamab is associated with significant clinical benefits and is cost-effective against previous SoC (PomDex, PanBorDex and SelDex).*[6] *Teclistamab is therefore anticipated to be used preferentially over these treatments in TCE RRMM patients in the 4L+ setting in UK clinical practice, as supported by UK clinical experts.* *Due to the recency of the recommendations for both teclistamab (November 2024) and elranatamab (December 2024, via the CDF), the population of 5L+ TCR-exposed patients in UK clinical practice is currently very small. This is consistent with the orphan designation status of talquetamab in this indication.*[7] *Given that the evidence base in 5L+ TCR exposed patients remains limited due to the rarity of the*	**The clinical evidence submitted by the company largely matches the patient population described in the final scope. No subgroups were considered. However, this is appropriate given the limitations of the evidence and small participant numbers (n=375 in the pivotal trial, n=154 in the cohort under consideration, see Section** Error! Reference source not found.**).** **It is unclear if the clinical evidence submitted by the company reflects the characteristics of the patient population in England and Wales eligible for treatment. Key trial evidence submitted for talquetamab contained no UK patients. The EAG were unable to verify whether the healthcare systems**

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment
			condition;[8] *and that teclistamab recently demonstrated clinical and cost-effectiveness benefits against the previous SoC treatment options available to TCR-exposed patients, the evidence does not permit the consideration of the subgroups based on prior T cell redirection therapy or prior lines of therapy.*	**across the recruiting 47 centres (located in Europe, Asia and North America) in the pivotal trial are comparable to NHS provision in terms of treatment pathways and availability of technologies.**
Intervention	Talquetamab	Talquetamab	*N/A*	**No EAG comment.**
Comparator(s)	• Panobinostat plus bortezomib and dexamethasone (PanBorDex) • Pomalidomide plus low-dose dexamethasone (PomDex) • Selinexor plus dexamethasone (SelDex) • Teclistamab • Isatuximab plus pomalidomide and dexamethasone (subject to NICE evaluation) • Belantamab mafodotin with pomalidomide and dexamethasone (subject to NICE evaluation) • Belantamab mafodotin with bortezomib and dexamethasone (subject to NICE evaluation)	Teclistamab	*The Company considers teclistamab [TA1015] to be the most relevant comparator for the purposes of decision making.*[6] *Teclistamab was recently recommended by NICE for routine commissioning for the treatment of RRMM in adults, only after 3 or more lines of treatment (including an IMiD, PI, anti-CD38 mAb) when the myeloma has progressed on the last treatment.*[6] *Prior to the recommendation of teclistamab, it was established that 'the main treatment that is used for RRMM myeloma after 3 or more lines of treatment was PomDex. If PomDex was not suitable,*	**The comparators described in the CS partially match the comparators described in the NICE Final Scope.** **Only one (Teclistamab) of seven potential comparators is included for appraisal.** **The EAG clinical advisers all agree that teclistamab is the most appropriate comparator for consideration.**

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment
			PanBorDex could be used. Additionally, if the myeloma is refractory to 4 or more treatments (i.e., in the 5L+ setting) SelDex was used'.[6] *Teclistamab significantly improves clinical outcomes for patients compared to PomDex, PanBorDex and SelDex, and was accepted to be cost-effective against these treatment options.*[6] *Therefore, teclistamab is expected to be used preferentially over these treatments in TCE RRMM patients in 4L+ TCE RRMM patients, and is the most relevant comparator for this submission, a view that is also aligned with those of clinical experts.* *The Company does not consider the following treatments to be relevant comparators:* • *PomDex (TA427), PanBorDex (TA380) and SelDex (TA970) are anticipated to have been displaced by teclistamab as a new SoC for NHS patients with 4L+ TCE RRMM, owing to its aforementioned benefits over these treatments.*	

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment
			• *Isatuximab with pomalidomide and dexamethasone (IsaPomDex) is not used in the population under consideration. Real-world evidence in the UK has confirmed that over 95% of IsaPomDex patients are anti-CD38 naïve and therefore would not be eligible to receive talquetamab.*[9] • *Belantamab mafodotin with bortezomib and dexamethasone (ID6212) and belantamab mafodotin with pomalidomide and dexamethasone (ID6211) are not relevant comparators to talquetamab in this setting. Both of these treatments are pending NICE guidance and therefore, are not considered as established in clinical practice in the NHS at the time of writing this submission.* *Further detail regarding the choice of comparator is provided in CS Table 3.*	

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment

Outcomes	The outcome measured to be considered include:
	• Overall survival (OS)
	• Progression-free survival (PFS)
	• Response rates
	• Time to next treatment (TTNT)
	• Adverse effects (AEs) of treatment
	• Health-related quality-of-life (HRQoL)
		Outcomes included in this submission are:
		• OS
		• PFS
		• Response rates:
		  ○ Overall response rate (ORR)
		  ○ Disease response
		  ○ Duration of response
		  ○ Time to response
		• Time to treatment discontinuation (TTD)
		• TTNT
		• AEs
		• Other:
		  ○ Minimal residual disease (MRD) negativity rate
			The write-up of the patient-reported outcomes (PRO) data from the pivotal trial informing the clinical effectiveness data for talquetamab (i.e., MonumenTAL-1) was not available in time for the submission deadline and therefore will not be presented. This data will be provided as an addendum when possible.
			
			However, as mentioned in CS Section 3.4.2, the EuroQoL Five Dimension Five Level Questionnaire (EQ-5D-5L) descriptive scores from MonumenTAL-1 (September 2024 data cut-off) were mapped onto the 3L UK value set to inform the economic model.
				The outcomes are largely similar with the addition of Minimal residual disease (MRD) - negativity rate. The EAG clinical advisors state that MRD is largely used within the context of research and not routinely used in practice across NHS centres.
				
				The EAG confirm that MRD was not included in the cost effectiveness analysis performed by the company (See Section 3.4.2)
				
				The EAG note that patient reported outcomes (PRO) were not initially included in the clinical evidence provided in the CS. However, EQ5D values from the pivotal trials for Talquetamab and Teclistamab were included in company model (See Section Error! Reference source not found. **and 3.4.9) PRO were provided as an addendum to the company**

	Final scope issued by NICE	Decision problem addressed in the company submission	*Rationale if different from the final NICE scope*	EAG comment
				clarification question responses.
Economic analysis	Not reported	Not reported	*Not reported*	**No EAG comment.**
Subgroups	Not reported	Not reported	*Not reported*	**No EAG comment.**
Special considerations	Not reported	Not reported	*Not reported*	**No EAG comment.**

2 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company (Johnson & Johnson) to support of the use of their technology, talquetamab (Talvey®).

2.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify relevant clinical evidence for the efficacy and safety of treatments for patients with RRMM who have received an IMiD, PI and an anti-CD38 antibody as part of their previous therapies (i.e. triple-class exposed patients, see Section 1.1.1). The original clinical SLR search was conducted on 26th May 2020 and updated on 22nd January 2021. All searches were subsequently updated in April 2022, May 2022, February 2023 and October 2023, with the most recent update conducted in December 2024. A detailed description of the SLR methods, eligibility criteria, searches, study inclusion/ selection, and data extraction performed for the SLR are provided in the CS Appendix B.

Overall, the EAG consider the SLR to be of reasonable quality, a summary is provided in Table 8.

Table 8. EAG appraisal of the CS SLR methods

Review process	EAG response	Key comments
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	**Yes**	See Table 7
Were appropriate sources searched?	**Yes**	See Section 2.1.1**Error! Reference source not found.**
Was the timespan of the searches appropriate?	**Yes**	See Section **Error! Reference source not found.**
Were appropriate search terms used?	**Yes**	See Section **Error! Reference source not found.**
Were the eligibility criteria appropriate to the decision problem?	**Partially**	In the December 2024 update, records including interventions other than talquetamab or teclistamab were deprioritised, by the company as no comparator other than teclistamab was considered relevant for their submission.

		The EAG note that these deprioritised records were neither data extracted, nor quality assessed.
Was study selection applied by two or more reviewers independently?	**Yes**	See Section 2.1.2
Was data extracted by two or more reviewers independently?	**Yes**	See Section 2.1.2
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	**Partially**	The company selected the Downs and Black checklist to assess study quality[10] The EAG considers that the Downs and Black checklist[10] was not the appropriate quality assessment tool to use because it considers studies with ≥2 treatment groups and the primary studies are single arms studies(see Sections 2.1.3.1.2, 2.1.5.1.1)
Was the quality assessment conducted by two or more reviewers independently?	**Yes**	See Section 2.1.2
Were attempts to synthesise evidence appropriate?	**Yes**	Indirect Treatment Comparisons (ITC) were performed. See Sections 2.2 and 2.3 for an overview and critique of the companies ITC. Note: The EAG quality assessed the ITC ROBINS-I for non-randomised studies and rated it as moderate risk of bias (See EAG Appendix and Section 2.2.1.4).
EAG; External Assessment Group; ITCs; indirect treatment comparison; ROBINS-I=Risk Of Bias In Non-randomised Studies of Interventions		

2.1.1 Searches

The searches excluded non-English studies which may not reflect the full scope of available research. CS Appendix B.1.1 describes the literature search sources and strategies. A good, appropriate selection of databases and other sources were searched, including clinical trials registries, websites of HTA agencies and

proceedings of recent conferences. The electronic database search strategies reported in CS Appendix 1-8 are broad, combining terms for TCE/pre-treated RR MM with study type filters only, without any intervention or comparator terms. Given the inclusion of most study types in the SLR (see CS Appendix B.1.2, Tables 13 and 14), the sensitivity of the MEDLINE and Embase searches could have been increased a little by not using study type filters, and only excluding unwanted publication types such as case reports, bibliographies, notes and editorials).

However, given the range of sources searched and additional checking of reference lists, the **EAG considers that no studies meeting the eligibility criteria are likely to have been missed by the literature searches.**

2.1.1.1 Inclusion criteria

The target population for the SLR included patients aged ≥18 years with RRMM who have received (i) at least one IMiD agent, (ii) at least one PI, and (iii) at least one anti-CD38 mAb (as per the MA, see Section 1.1). Initially, eligible interventions were treatments under investigation for RRMM provided as a single-agent or a combination treatment (CS Appendix B, Table 13). The EAG note that for the December 2024 update, the interventions included in the eligibility criteria were narrowed in line with the anticipated scope for the submission (CS Appendix B, Table 14).

Ultimately, teclistamab was selected as the only relevant comparator and studies reporting on talquetamab and teclistamab were prioritised for data extraction.[11-13] Despite some concerns about the search method and inclusion criteria, the **EAG considers it unlikely that any relevant studies have been missed**. This is because the eligibility criteria for this appraisal are narrow in terms of population (line of therapy) and interventions of interest.

2.1.2 Study selection

The company adopted a systematic approach to select relevant studies. Abstract and full text screening were conducted by two independent reviewers and disagreements were resolved by the involvement of a third researcher. Similarly, data extraction was performed by a single reviewer and independently assessed for accuracy and completeness by a second reviewer. Disagreements were resolved by a third independent reviewer when necessary. The following specific data types were extracted: publication characteristics, study setting, study methods, participant demographics (such as number and type of prior LOTs, age, sex, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status score and time since diagnosis) and study findings. Detailed characteristics of included studies are provided in CS Table 15, Appendix B.

2.1.2.1 Original SLR and updates to October 2023

The original SLR included 455 publications reporting on 218 unique studies. The company provided a list of included studies (CS, Appendix B, Page 58, Table 15 in embedded document) and excluded studies (CS, Appendix B, Page 58, Table 16 in embedded document).

2.1.2.1.1 SLR update

In total, 122 publications reporting on 23 unique studies on talquetamab or teclistamab were selected for extraction for the purposes of this submission. (28 studies were included in the SLR and reasons for the deprioritised studies were provided in response to CQ A.5 [Table 8]).The company did not provide detailed study characteristics for all the 121 publications in the original CS. CS Appendix Table 15 suggests that the 23 included were primary publications and other publication types (i.e., conference abstracts, trial registry records, etc) may have been consulted if any other data missing. The EAG was unable to ascertain why detailed information was only provided for 23 publications (see in Table 15 CS Appendix B, section 1.3, Page 63). Critical appraisal of the non-randomised trials and observational studies included in the SLR update, using the modified Downs and Black checklist[10] is provided in CS Table 20 and Table 21, Appendix B. All the included studies were rated by the company to be at high risk of bias for at least one risk of bias domain. EAG ratings of CS evidence are provided later in Sections 2.1.3.1.2 and 2.1.5.1.1

The number of participants randomised or enrolled in 23 studies ranged from 14-288 (see CS Appendix Table 15). The EAG note that **none of these 23 studies included a UK population**. Key response outcomes (overall response rate [ORR] and duration of response [DoR]) and survival outcomes (OS and PFS) reported by studies included in the SLR update are presented in CS Table 16 and Table 17, Appendix B. Of the 23 studies, only two studies, (MonumenTAL-1 and MajesTEC-1), were selected by the company as relevant evidence for the submission (See Section 2.2). Upon clarification, the company stated that, of the four interventional studies identified in the SLR, only MonumenTAL-1 and MajesTEC-1 were selected as relevant by the company as the other two studies had a small sample size (NCT05972135, N=6 participants) or focused on a Japanese population (NCT04696809, N=40 participants).[14, 15]

Seventeen real-world evidence (RWE) studies were not selected for inclusion in the submission, because they "*represented a lower grade of empirical evidence*" (CS Section 2.1). Whilst these studies were included in the SLR they were disregarded in the CS, which the EAG consider to be potentially unjustified. These observational studies might have been used by the company to examine the robustness of the results of the company ITC, and the EAG has been able to include some of this work

in this report to explore uncertainty in the effect estimates of the indirect treatment comparison (see Section 2.2.7, and see also Section 3.4.7.5 for EAG additional analysis exploring uncertainty in company OS HR via RWE).

2.1.3 Clinical effectiveness evidence

The clinical evidence presented in the CS for talquetamab and relevant comparator treatment (teclistamab) was obtained from two data sources (MonumenTAL-1 and MajesTEC-1).[11-13]

Since no studies were identified in the SLR directly comparing talquetamab with teclistamab, the company used the IPD from the MajesTEC-1 trial to represent the most appropriate data source for teclistamab to inform the comparative efficacy evidence in this submission. EAG trial critique is provided in the ITC Section 2.2. Brief summaries are provided below.

2.1.3.1 Talquetamab (intervention)

The most relevant study identified in the clinical SLR that investigated the efficacy and safety of talquetamab as a treatment for adult patients with TCE RRMM was the MonumenTAL-1 trial.[11, 12]

2.1.3.1.1 Overview of MonumenTAL-1

MonumenTAL-1 is a single-arm, open-label, multicentre phase 1–2 study of talquetamab.[11, 12] The trial comprised two phases: phase I (part 1: dose escalation, part 2: dose expansion) and Phase II (part 3: dose expansion). The subcutaneous (SC) doses of 0·4 mg/kg once a week and 0·8 mg/kg every two weeks were identified in phase I and were evaluated in phase II in patients who were 18 years of age or older, had at least three previous lines of therapy including at least one IMiD, one PI, and an anti-CD38 mAb (TCE), had an Eastern Cooperative Oncology Group performance status of 0 to 2, and were naive or exposed to previous T-cell redirection therapy (TCR).

Patients were recruited from 47 centres across Europe, Asia and North America. **The study did not recruit any patients from the UK**. Most patients were white (81.8%) with a median age of 67 years.[16] The lack of UK patients limits the applicability of the results in terms of representativeness and generalisability for the UK context given differences in healthcare systems and practices especially including subsequent treatments in the 47 recruiting centres. Given the single-arm, open-label design of MonumenTAL-1, there was no control arm to allow for direct evaluation versus a comparator. The EAG consider these key issues for consideration in the appraisal (see Table 1).

Cohorts in MonumenTAL-1

The MonumenTAL-1 trial comprised several cohorts that included different patient populations and talquetamab dosing regimens (see CS Section 2.3.1 for more detail).

- Cohort A (patients without prior TCR exposure) 0.4 mg/kg once a week SC talquetamab
- Cohort B (patients with prior TCR exposure): 0.4 mg/kg once a week or 0.8 mg/kg every two weeks SC talquetamab
- Cohort C (patients without prior TCR exposure): 0.8 mg/kg every two weeks SC talquetamab.

Of these cohorts the company suggest that **Cohort C provides the most relevant source of evidence for talquetamab in this submission.** In Cohort C, 154 patients received 0.8 mg/kg talquetamab every two weeks. The CS states that Cohort C was validated via clinical feedback obtained by the company and the RealiTAL RWE study.[17, 18] Company clinical experts also suggested that every two weeks dosing in Cohort C is associated with a lower incidence of adverse events than in Cohort A who experienced weekly SC dosing (CS Section: 2.11 section and Appendix L). EAG clinical experts agree that Cohort C (0.8 mg/kg SC every two weeks) most likely reflects anticipated UK practice as "*patients would need to spend less time at the treatment centre*". The company stated that clinical feedback confirmed that the vast majority (90%) of patients in UK clinical practice will likely receive this regimen.

The company considered Cohort C as the most relevant evidence for the appraisal given improved convenience for patients (less burden due to less frequent hospital visits, associated with the fortnightly dosing regimen in Cohort C (every two weeks SC) compared to the weekly dosing regimen in Cohort A (weekly SC). The EAG clinical advisor reflected that UK Centres are more likely to choose only one treatment protocol (0.4 mg/kg every week SC or 0.8 mg/kg every two weeks) given the capacity constraints in hospital pharmacies. However, it is worth noting that the prior lines of therapy in Cohort C ranged from [redacted], with a median of [redacted]. EAG clinical advisors suggest that the increased number of prior therapies received by patients in MonumenTAL-1 may not fully reflect the complex NHS treatment landscape for MM (see Figure 1).

Baseline characteristics of these patients were reported in CS Section 2.3.3 (CS Table 7; Page 53). The EAG compared the patient characteristics with the patient population in MajesTEC-1 (See Table 14) A full critique of MajesTEC-1 was provided in TA1015.[6] The EAG suggest that the patient characteristics were largely comparable between these two groups with the following differences identified in MonumenTAL-1

- Greater proportion of patients aged ≥75 in the MonumenTAL-1 study than in the MajesTEC-1 ([redacted]% compared to 14.5%, respectively).

- Higher proportion of patients with International Staging System ([ISS] classification system) stage III disease (24.4% in MonumenTAL-1 compared to 12.3% in MajesTEC-1).

- Higher proportion of patients with extramedullary plasmacytomas (myeloma cells which form outside the bone) (26.6% had ≥1 in the MonumenTAL-1 study compared to 17.0% in the MajesTEC-1 study).

The company state that these characteristics suggest that patients receiving talquetamab are harder to treat and have more advanced disease than those receiving teclistamab.[19] The EAG clinical advisors suggested that participants included in both the MonumenTAL-1 and MajesTEC-1 studies were less unwell than patients they may treat in NHS services, who tend to be "*sicker and more frail*" than those included in trials.

Cohort B has its own limitation as this group includes patients with prior TCR exposure (73.1% received CAR-T therapies), which are not currently available to NHS patients with TCE RRMM. The EAG clinical advisor agreed that CAR-T therapies are available to patients as part of ongoing studies, but not via routine NHS care.

Consequently, the company selected Cohort C IPD (n=154) from the MonumenTAL-1 study to provide the evidence for talquetamab in the ITC analysis which is critiqued in Section 2.2

Efficacy endpoints

The efficacy endpoints evaluated in MonumenTAL-1 trial included; response rates (overall, duration of response [DoR], stringent complete response [sCR], complete response or better [≥CR], very good partial response or better [≥VGPR]), overall survival [OS], progression-free survival [PFS], time-to-next-treatment [TTNT], time to treatment discontinuation [TTD], minimal residual disease [MRD] negativity rate, number of patients with adverse events [AEs], number of patients with severe adverse events [SAEs] and health-related quality of life [HRQoL]. The trial endpoints which informed the company economic model are reported in detail in Section 3.4.5 and displayed in Table 15 below. At the clinical cutoff, [redacted]% of participants had discontinued study participation. As of the September 2024 data cut off (DCO), 17.5 of patients remained on talquetamab treatment. Progressive disease was the primary reason for talquetamab discontinuation ([redacted]%). Patient withdrawals are detailed in CS Section 2.4.1 (CS Table 9; Page 61).

The company claim that the efficacy data observed in the MonumenTAL-1 trial is likely to represent a conservative underestimate of the true efficacy of talquetamab in TCE RRMM patients, however, supportive direct comparative evidence in NHS populations is lacking. The EAG conducted exploratory analysis of the efficacy of

talquetamab using observational studies (Real World Evidence in non-UK settings [RWE]) to investigate the plausible true efficacy of talquetamab (see Section 3.4.6).

2.1.3.1.2 Risk of bias MonumenTAL-1

Critical appraisal of MonumenTAL-1 was carried out using the modified Downs and Blacks checklist for non-randomised trials.[10] The checklist includes 27 questions, covering the concepts of study reporting, external validity, bias, confounding, and power. The results from the quality assessment are presented in the CS Table 14.

The EAG agrees with most of the company's judgements. Overall, the trial was a well-designed single arm trial with the appropriate steps taken to minimise bias where possible. The trial was deemed to be at low risk of bias across most of the domains. Of those marked as high risk, the majority were factors inherent to the design of a single-arm trial (for example, blinding of participants and outcome assessors).

A comparison of the company's assessment and the EAG's assessment of risk of bias in the trial using NICE recommended criteria can be seen in Table 9.

Table 9. Comparison of company and EAG risk of bias assessment of MonumenTAL-1

Question	Company Assessment	EAG Assessment
MonumenTAL-1		
1) Is the hypothesis/aim/objective of the study clearly described?	Yes	**Yes**
2) Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	**Yes**
3) Are the characteristics of the patients included in the study clearly described?	Yes	**Yes**
4) Are the interventions of interest clearly described?	Yes	**Yes**
5) Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes	**NA-single arm trial**
6) Are the main findings of the study clearly described?	Yes	**Yes**
7) Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	**Yes**
8) Have all important adverse events that may be a consequence of the intervention been reported?	Yes	**Yes**

9) Have the characteristics of patients lost to follow-up been described?	Yes	**Yes**
10) Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is < 0.001?	Yes	**Yes**
11) Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	**Yes**
12) Were those patients who were prepared to participate representative of the entire population from which they were recruited?	Yes	**Yes**
13) Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes	**Yes**
14) Was an attempt made to blind study patients to the intervention they have received?	No	**No- the study was an open label trial and blinding was not attempted**
15) Was an attempt made to blind those measuring the main outcomes of the intervention?	No	**No- the study was an open label trial and blinding was not attempted**
16) If any of the results of the study were based on "data dredging", was this made clear?	Yes	**Yes- no data dredging suspected**
17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	**Yes- one treatment group relevant; median follow-up (and range) reported for all cohorts, and Kaplan Meier used for survival**
18) Were the statistical tests used to assess the main outcomes appropriate?	Yes	**Appropriate statistical analyses were used**
19) Was compliance with the intervention/s reliable?	Yes	**Yes- compliance with study drug reported in the CSR and the economic model takes this into account**

20) Were the main outcome measures used accurate (valid and reliable)?	Yes	**Yes- outcomes measures were acceptable and reliable**
21) Were the patients in different intervention groups recruited from the same population?	Yes	**Yes**
22) Were study patients in different intervention groups recruited over the same period of time?	NA	**NA- single arm trial**
23) Were study patients randomised to intervention groups?	No	**NA- single arm trial**
24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	**NA- single arm trial**
25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	NA	**NA- single arm trial**
26) Were losses of patients to follow-up taken into account?	Yes	**Yes, losses to follow up were reported in the CSR**
27) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?	Yes	**Yes, the study had sufficient power to detect a clinically important effect. Statistical power calculations were described in the CSR and appropriate.**

2.1.4 Statistical approach adopted for the analysis of the MonumenTAL-1

In addition to information provided in the CS, information relevant to the statistical approach taken by the company to analyse the MonumenTAL-1 trial data has been extracted from the clinical study report (CSR) the trial statistical analysis plan and the trial protocol. The EAG considers that the statistical approaches adopted by the company were appropriate (Table 10).

Table 10. Statistical approach used in MonumenTAL-1

Item	EAG Assessment (Y/N)	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Y	Of the patients in the All Treated Analysis Set, only patients in Cohort C (0.8 mg/kg Q2W) are of relevance to this submission.
Was an appropriate sample size calculation pre-specified?	Y	The sample size for Cohort C was determined by assuming that the observed ORR for talquetamab was at least [redacted]%. If that assumption was true, there would be more than 85% power to declare that the ORR was higher than 30% at the one-sided significance level of 0.025
Were all protocol amendments made prior to analysis?		
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Y	Analysis of the primary endpoint, ORR, was based on the 'all treated analysis set'. The ORR and its 2-sided 95% exact CI for each cohort were presented. The key secondary efficacy endpoints included DoR, VGPR or better/CR or better/sCR as defined by the IMWG response criteria, TTR, PFS, OS, MRD negativity status and ORR. The distribution of DoR was estimated using the Kaplan-Meier method Time to first response was analysed for patients who achieved a response (PR or better), and descriptive statistics (N, mean, SD, median, and range) were provided for each cohort. Time to best response, time to CR or better response, and time to VGPR or better response were summarised similarly. Analysis was performed based on IRC assessment. Analysis of PFS was based on the 'all treated analysis set'. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each cohort. The median PFS with 95% CI was provided. Overall survival was analysed using similar statistical methods as described for PFS analysis. The MRD negative rate and its 2-sided 95% exact CI were presented for each cohort. The threshold value of 10-5 was used for the primary MRD negativity analysis. All safety analyses were based on 'all treated analysis set', and analysed using descriptive statistics. HRQoL assessments were analysed using descriptive statistics.

Was the analysis approach for PROs appropriate and pre-specified?	Y	The company noted that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline and therefore not presented. Stating, It will be provided as an addendum when possible. The PRO data were provided as an addendum to the clarification question responses.
Was the analysis approach for AEs appropriate and pre-specified?	Y	All safety analyses were based on 'all treated analysis set'. The number, mean, standard deviation, median, minimum and maximum were calculated for all continuous safety variables. For categorical variables, frequency counts and percentages were reported.
Was a suitable approach employed for handling missing data?	N	For MonumenTAL-1 Cohort C, no data imputation was performed.
Were all subgroup and sensitivity analyses pre-specified?	Y	Subgroup analyses for ORR were stratified by using the appropriate statistical methods

2.1.5 Adverse events

[redacted] patients in Cohort C of the MonumenTAL-1 trial (cohort considered relevant to this appraisal) experienced at least one treatment-emergent adverse event (TEAE), with [redacted]% of patients experiencing at least one TEAE that was related to talquetamab.

Serious TEAE(s) were reported in [redacted]% of patients, and [redacted]% of patients in Cohort C were judged by the investigator to have experienced serious TEAEs that were related to talquetamab. Maximum Grade 3 TEAE(s) were reported for [redacted]%, maximum Grade 4 TEAE(s) were reported for [redacted]% of patients and maximum Grade 5 TEAE(s) were reported for [redacted]% of patients. Additionally, [redacted]% of patients experienced a TEAE with an outcome of death.

During clarification (CQ A.2) The company acknowledged that the number of TEAEs leading to discontinuation, Grade 4 AEs, Grade 5 AEs and TEAEs leading to death were higher in Cohort C compared to Cohort A. However, the overall incidence of TEAEs related to talquetamab, serious TEAEs, serious TEAEs related to talquetamab and Grade 1–3 TEAEs were lower in Cohort C compared to Cohort A.

Further details (outcomes and adverse events) are provided in the EAG critique Section 2.2.6.

2.1.5.1 Teclistamab (comparator/TA1015)

MajesTEC-1 is a Phase I/II, open-label, single-arm, international, multicentre study investigating the safety and efficacy of teclistamab as a monotherapy in adult patients with TCE RRMM.[13] The primary endpoint was ORR, with key secondary endpoints including OS and PFS.[13] Patients who received the Recommended Phase 2 Dose (RP2D) of teclistamab, referred to as the "All Treated Analysis Set (N=165)" informed the comparative efficacy evidence of teclistamab versus talquetamab (see Section 2.2.1). This was based on the final prespecified DCO of August 2023, with a median follow-up of 30.4 months, which also informed TA1015 (See Table 7).[6]

The MajesTEC-1 study population consisted of three cohorts A, B and C (see Table 13). Cohort A contained patients with RRMM who had received ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb (TCE). Cohort B included more heavily pre-treated patients who had experienced at least 4 lines of treatment and was not open for enrolment. Cohort C included patients who had previously received an anti- B-Cell Maturation Antigen (BCMA) (including CAR-T therapy) treatment. A summary of the study is presented in CS Table 23 (page 93) and full details, including the methods, baseline characteristics and study results, are presented in CS Appendix B.

The EAG note that during TA1015[6] UK clinical experts deemed the MajesTEC-1 trial to be generalisable to UK clinical practice and the Committee accepted the trial as an appropriate source of clinical effectiveness evidence for teclistamab in TCE RRMM patients.[6]

2.1.5.1.1 Risk of bias in the MajesTEC-1 trial

A quality assessment of the MajesTEC-1 study was conducted by the company using the modified Downs and Black checklist.[10] Overall, the study was considered to be at low risk of bias for the majority of the domains. **The EAG agrees with the majority of the company's ratings**. However, we were unable to determine whether losses to follow-up were taken into account and addressed in the analyses.

A comparison of the EAG's and company's assessment is reported in the Table 11.

Table 11: Comparison of company and EAG risk of bias assessment in MajesTEC-1

Question	Company Assessment	EAG Assessment
MajesTEC-1		
1) Is the hypothesis/aim/objective of the study clearly described?	Yes	**Yes**
2) Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	**Yes**

3) Are the characteristics of the patients included in the study clearly described?	Yes	**Yes**
4) Are the interventions of interest clearly described?	Yes	**Yes**
5) Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes	**NA-single arm trial**
6) Are the main findings of the study clearly described?	Yes	**Yes**
7) Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	**Yes**
8) Have all important adverse events that may be a consequence of the intervention been reported?	Yes	**Yes**
9) Have the characteristics of patients lost to follow-up been described?	Yes	**Yes**
10) Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is < 0.001?	Yes	**Yes**
11) Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	**Yes**
12) Were those patients who were prepared to participate representative of the entire population from which they were recruited?	Yes	**Yes**
13) Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes	**Yes**
14) Was an attempt made to blind study patients to the intervention they have received?	No	**No- the study was an open label trial and blinding was not attempted**
15) Was an attempt made to blind those measuring the main outcomes of the intervention?	No	**No- the study was an open label trial and blinding was not attempted**
16) If any of the results of the study were based on “data dredging”, was this made clear?	Yes	**Yes- no data dredging suspected**
17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	**Yes- one treatment group relevant; median follow-up (and range) reported for all cohorts, and Kaplan Meier used for survival**
18) Were the statistical tests used to assess the main outcomes appropriate?	Yes	**Appropriate statistical analyses were used**

19) Was compliance with the intervention/s reliable?	Unclear	**Unable to determine**
20) Were the main outcome measures used accurate (valid and reliable)?	Yes	**Yes- outcomes measures were acceptable and reliable**
21) Were the patients in different intervention groups recruited from the same population?	Yes	**Yes**
22) Were study patients in different intervention groups recruited over the same period of time?	NA	**NA- single arm trial**
23) Were study patients randomised to intervention groups?	No	**NA- single arm trial**
24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	**NA- single arm trial**
25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	NA	**NA- single arm trial**
26) Were losses of patients to follow-up taken into account?	Yes	**Unable to determine**
27) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?	Yes	**Yes, the study had sufficient power to detect a clinically important effect.**

2.2 Critique of trials identified and included in the indirect comparison

As detailed in Section 2.1.3, only two single arm studies, (MonumenTAL-1[11, 12] and MajesTEC-1[13]) were selected by the company as relevant evidence for the submission. Because of the lack of comparators for both talquetamab and teclistamab, the EAG agree with the company that a conventional pair-wise meta-analysis is not possible. In the absence of randomised controlled trials and with no common comparator, network meta-analysis (NMA) and anchored matched adjusted indirect comparison (MAIC) were also not feasible.

To generate effect estimates to include in the economic model (see Section 3.4.5), the company conducted an indirect treatment comparison (ITC) using IPD from the MonumenTAL-1 and MajesTEC-1 studies to compare the clinical efficacy and safety of talquetamab and teclistamab. The EAG note that the Company own both talquetamab and teclistamab and therefore, were able to access IPD for both studies, however, the IPD was not submitted for EAG critique as part of the appraisal.

2.2.1 ITC data sources

Study design features of MonumenTAL-1 and MajesTEC-1 trials are compared in Table 14.

2.2.1.1 MonumenTAL-1

MonumenTAL-1 commenced in 2018, and the data provided in the CS are based on a pre-specified DCO of September 2024. The trial population consists of three cohorts which represent a combination of patients from Phases I (part 2) and II (part 3) who received SC talquetamab at the recommended Phase 2 dosing level (RP2D) only Cohort C informed the ITC (see Table 12).

The efficacy outcomes reported for the MonumenTAL-1 study estimated in the ITC analysis were overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Table 12: MonumenTAL-1 study patient cohorts.

Patient cohort, prior TCR exposure	**Dose of talquetamab**	**Phase, part # (sample size)**
Cohort A - No prior TCR exposure	0.4 mg/kg weekly SC	Phase I, part 2 (n=[redacted]) Phase II, part 3 (n=[redacted]) Total sample (n=143)
Cohort B - Prior TCR exposure	0.4 mg/kg weekly SC or 0.8 mg/kg every two weeks SC	Phase I, part 2 (n=[redacted]) Phase II, part 3 (n=[redacted]) Total sample (n=78)
Cohort C - No prior TCR exposure	**0.8 mg/kg every two weeks SC**	**Phase I, part 2 (n=[redacted]) Phase II, part 3 (n=[redacted]) Total sample (n=154)**
RP2D=recommended phase-2 dose; TCR=T-cell receptor therapy; RRMM=relapsed and refractory multiple myeloma; SC=subcutaneous. **BOLD: Cohort included in the ITC**		

2.2.1.2 MajesTEC-1 ITC Cohort A and Phase 2 dosing level (RP2D) sample

MajesTEC-1 consisted of three cohorts A, B and C (see Section 2.1.5.1) the IPD from the 'All Treated Analysis Set' sample (N=165), i.e., the combination of Cohort A (n=125) and the RP2D sample (n=40) from Phase I (part 2) were used to inform the assessment of comparative clinical efficacy for teclistamab versus talquetamab in the ITC analysis (Table 13).

Table 13: MajesTEC-1 study patient cohorts.

Patient cohort, prior TCR exposure	Dose of teclistamab	Phase, part # (sample size)
RP2PD sample - No prior TCR exposure (patients with RRMM TCE)	**RP2PD 1.5 mg/kg weekly SC**	**Phase I, part 2 (n=40)**
Cohort A - No prior TCR exposure (patients with RRMM TCE)	**RP2PD 1.5 mg/kg weekly SC**	**Phase II, part 3 (n=125)**
Cohort B - No Prior TCR exposure Heavily pre-treated patients considered penta-drug refractory	**RP2PD 1.5 mg/kg weekly SC**	Phase II, part 3 (n=0)
Cohort C - Prior TCR exposure	**RP2PD 1.5 mg/kg weekly SC**	Phase II, part 3 (n=40)

RP2PD=recommended phase-2 dose; T-cell receptor therapy; RRMM=relapsed and refractory multiple myeloma; Q2W=biweekly; QW=weekly; SC=subcutaneous **BOLD: Cohorts included in the ITC**

The key efficacy outcomes (e.g., ORR, DOR, PFS, OS) informing this appraisal for talquetamab from MonumenTAL-1 were also reported for the MajesTEC-1 trial (See Table 14), therefore these were the endpoints assessed in the ITC analysis. The key efficacy outcome included from the ITC included in the economic model was OS HR (See Section 3.4.5) however, the EAG have concerns about the reliability of the effect estimates (OS, PFS) from the ITC. This is detailed further in Section 2.2.7

2.2.1.3 EAG comparison of study design features of MonumenTAL-1 and MajesTEC-1 trials

The EAG list and qualitatively compare various study features between the MonumenTAL-1 and MajesTEC-1 trials in Table 14.

Overall, the EAG suggests that the populations in both the MonumenTAL-1 and MajesTEC-1 trials included were broadly representative of the target population of TCE RRMM patients seen in routine UK practice as described in the NICE Final Scope (see Table 7). It is worth noting that both trials were designed as international multicenter studies, however, only the MajesTEC-1 trial recruited UK patients (n=[redacted]). Moreover, the sample included predominantly White ([redacted]%), followed by Black or African American ([redacted]%) and Asian ([redacted]%) participants. According to the company, subjects with African heritage experience MM at twice the frequency as Caucasians.

Table 14: Selected design and methodological features of MonumenTAL-1 and MajesTEC-1.

Study feature	MonumenTAL-1 trial (Talquetamab) IPD Phase I (NCT03399799) Phase II (NCT04634552) [n=154]	MajesTEC-1 trial (Teclistamab) IPD Phase I (NCT03145181) Phase II (NCT04557098) [n=165]	Comparability (EAG assessment: Yes or No)
Study design	A Phase I/II international, open-label, multicentre, single-arm trial assessing the safety and efficacy of talquetamab monotherapy. Phase I (Parts 1-2): dose escalation and expansion Phase II (Part 3): patients receiving RP2D. Phase I part 2/Phase II part 3 Cohort A: n=143 Cohort B: n=78 Cohort C: n=154	Phase I/II international, open-label, multicentre, single-arm trial assessing the safety and efficacy of teclistamab monotherapy. Phase I (Parts 1-2): dose escalation and expansion Phase II (Part 3): patients receiving RP2D. Phase I part 2 Cohort RP2D: n=40 Phase II part 3 Cohort A: n=125 Cohort B: n=0 Cohort C: n=40	**Yes (clinical trial vs. clinical trial)**
Study setting	4L+ setting (≥3 prior therapies: IMiD, PI and anti-CD38 mAb)	4L+ setting (≥3 prior therapies: IMiD, PI and anti-CD38 mAb)	**Yes**
Locations	47 centres (Belgium, France, Germany, Israel, the Netherlands, Poland, Republic of Korea, Spain, and the US)	35 centres (France, Netherlands, the US, the UK, Belgium, Germany, Italy, Spain, Sweden, Canada, China)	**Yes (both trials multicentre, multinational, however no UK patients)**

Study population inclusion criteria	TCE adult (≥18 years of age) patients with measurable RRMM diagnosis according to IMWG (i.e., received ≥3 prior treatments including at least one IMiD, PI and anti-CD38 mAb) ECOG PS score 0-1 (Phase 1) or 0-2 (Phase 2)	TCE adult (≥18 years of age) patients with measurable RRMM diagnosis according to IMWG (i.e., received ≥3 prior treatments including at least one IMiD, PI and anti-CD38 mAb) ECOG PS score 0-1	**Yes**
Study population exclusion criteria	Prior TCR (including CAR-T) exposure, GPRC5D targeting therapy, grade ≥3 CRS following prior TCR therapies, vaccinated with live/attenuated vaccine, unresolved toxicities from previous anticancer therapies (Grade>1) except for alopecia or peripheral neuropathy, received dose of corticosteroids ≥140 mg within the 14-day period before the first dose of study drug, stroke or seizure within six months prior to signing the informed consent form.	Prior TCR including BCMA-targeting therapy.	**Yes**
Intervention (dose, mode, schedule)	0.8 mg/kg SC Q2W Talquetamab monotherapy was administered to patients until disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study (defined as two years after the last patient had received the initial dose of talquetamab or when the last patient had completed the last study assessment in the study, whichever occurred first).	1.5 mg/kg SC Q1W Teclistamab monotherapy was administered until disease progression, unacceptable toxicity, withdrawal of consent, death, or the end of the study (defined as two years after the last patient's first dose or when the last patient had completed the last study assessment in the study, whichever occurred first).	**Yes**
Comparator	None (single-arm study)	None (single-arm study)	**Yes**
Primary outcome	ORR	ORR	**Yes**
Secondary outcome	DOR, ≥VGPR, ≥CR, sCR, TTR, PFS, TTNT, OS, MRD negativity rate, # of	DOR, ≥VGPR, ≥CR, sCR, TTR, PFS, TTNT, OS, MRD negativity rate, # of	

	patients with AEs/SAEs, change from baseline in HRQoL (EORTC QLQ-C30, EQ 5D-5L, PGIS)	patients with AEs/SAEs, PR, change from baseline in HRQoL (EORTC QLQ-C30, EQ 5D-5L VAS scores)	
Subsequent treatments (most frequent)	N=[redacted] <u>UK relevant</u> Teclistamab ([redacted]) <u>Non-UK relevant</u> Carfilzomib + chemotherapy ([redacted]), Belantamab-based regimens ([redacted]), CAR-T cell therapies ([redacted]), Dexamethasone-based regimens ([redacted])	N=[redacted] <u>UK relevant</u> Bortezomib + chemotherapy ([redacted] <u>Non-UK relevant</u> Investigational antineoplastic drugs ([redacted]), Talquetamab ([redacted]), Pomalidomide based regimens ([redacted]), Carfilzomib + chemotherapy ([redacted]), CAR-T cell therapies ([redacted]	**No**
Duration of study follow-up	September 2024 DCO The first patient in the study was treated on 3rd January 2018 and at the latest DCO the median duration of follow-up was 31.2 months for Cohort C (n=154)	August 2023 DCO The first patient in the study was treated on 16th May 2017, and at the latest DCO, the median duration of follow-up: 30.4 months (range: 0.3-41.5 months) for the All Treated Analysis Set (n=165).	**Yes**
Statistical analysis	The analysis of ORR was based on the 'all treated analysis set'. The ORR and its 2-sided 95% CIs for each cohort were presented. A forest plot analysis of ORR for a priori defined subgroups (e.g., age, sex, race, ECOG PS, lines of treatment, ASCT, type of myeloma, tumour GPRC5D expression, cytogenetic risk, and other baseline characteristics) was conducted. The Kaplan-Meier method was used to estimate the	The ORR and associated two-sided 95% CIs were calculated. The ORRs were also compared across various a priori defined subgroups (e.g., cytogenetic risk, refractory status, and number of previous lines of therapy). The Kaplan–Meier method was used to estimate time to-event end points (DOR, PFS, and OS).[20]	**Yes**

	OS, PFS, DOR, TTR, TTD. HRQoL assessments were analysed using descriptive statistics.		
Power calculation	The sample size for Cohort C was determined by assuming that the observed ORR for talquetamab was at least 45%. If that assumption was true, there would be more than 85% power to declare that the ORR was higher than 30% at the one-sided significance level of 0.025	Sample size of 100 patients would provide a power of at least 85% to establish an ORR>30% at a one-sided significance level of 0.025, assuming an ORR≥45%.[20]	**Yes**
ITC analysis	Cohort C [n=154] (Phase II part 3 cohort n=118 and Phase I part 2 RP2D cohort n=36) was included in the ITC analysis (Cohorts A and B were excluded as not relevant to UK clinical routine practice).	All Treated Analysis Set [n=165] (Phase I part 2 RP2D cohort n=40 and Phase II part 3 Cohort A n=125) was included in the ITC analysis (Cohorts B and C were excluded as not relevant to UK clinical routine practice).	**No**

IPD=individual patient data; EAG=evidence appraisal group IMWG= International Myeloma Working Group; ECOG PS= Eastern Cooperative Oncology Group Performance Status; NR-not reported; CDF=cancer drug fund; AEs=adverse events; SAE=serious adverse event; CR=complete response; DoR=duration of response; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EQ-5D-5L=European Quality of Life Five Dimension Five Level Questionnaire; HRQoL=health-related quality of life; IMiD=immunomodulatory drug; IV=intravenous; mAb= monoclonal antibody; MRD=minimal residual disease; N/A=not applicable; NCT=National Clinical Trial; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PGIS=Patient Global Impression of Severity; PI=proteasome inhibitor; Q2W=once every two weeks; QW=once weekly; RRMM=relapsed or refractory multiple myeloma; RP2D=recommended phase-2 dose; sCR=stringent complete response; PR= partial response; SC=subcutaneous; SoC=standard of care; TCE=triple-class exposed; TCR=T-cell redirecting therapy; TTD=time to treatment discontinuation; TTR=time to response; TTNT=time to next treatment; VGPR=very good partial response; DLT=dose-limiting toxicity; mos=months; DCO=data cut-off; L=line of treatment; CAR-T=chimeric antigen receptor T-cell; GPRC5D=G protein coupled receptor class 5D; CRS=cytokine release syndrome; ASCT=autologous stem cell transplant; ISS=International Staging System; ADC= antibody-drug conjugate; ITC=indirect treatment comparison; BCMA=B cell maturation antigen

Overall, the definition of efficacy outcomes used in the company ITC analysis is likely to be comparable between MonumenTAL-1 and MajesTEC-1 trials, as both were conducted by the same company about one year apart in time. In terms of the outcome assessment, the length of follow-up was sufficient and similar between the two trials (median: 30-31 months). However, there were differences between trials (described in Section 2.2.7) which the EAG consider important for consideration by the committee.

- The EAG highlight that as both evidence sources were open label trials knowledge of the treatment of study participants, study personnel, and

outcome assessors is likely to bias the measurement of the study outcomes (response rate, disease progression, PFS), however these outcomes were based on established International Myeloma Working Group (IMWG) criteria and this may reduce bias.
- In addition, the measurement of OS relies on mortality data, which is an objective endpoint, free of subjective interpretation.

2.2.1.4 Critical appraisal of the ITC of MonumenTAL-1 and MajesTEC-1 trials

The company used a *modified 27-item Downs and Blacks checklist* for non-randomised trials[10] to critically appraise the MonumenTAL-1 and MajesTEC-1 trials regarding study reporting, external validity, bias, confounding, and power. The results from the quality assessment are presented in Section 2.1.5.1.1 of this report, as well as CS document (CS Table 14) and Appendix B.1.8 (CS Table 28).

- In brief, the company rated both studies as being at **low risk of bias** for reporting quality (10 items: #1-10), external validity (3 items: #11-13), outcome measurement/ ascertainment (5 items: #16-20), losses to follow-up (1 item: #26), and study power (1 item; #27).
- There were only two items rated as being at **high risk of bias** for the domain of outcome assessment: blinding of patients (item 1: #14) and blinding of outcome assessors (1 item: #15).

The EAG assessed the risk of bias (and quality of the ITC analysis) using The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool[21] (a copy is provided in the EAG Appendix). This tool covers the assessment of 7 risk of bias domains: i) confounding, ii) selection of participants into the study, iii) classification of interventions, iv) deviations from intended interventions, v) missing data, vi) measurement of outcomes, and vii) selection of the reported result.

The EAG judged the ITC to be **low risk of bias for 5/7 domains of bias** (selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, and measurement of outcomes). Two domains (2/7) of "Confounding" and "Bias in selection of the reported result" however were judged to be at **moderate risk of bias overall.** It is however worth mentioning that the company and EAG assessments are not directly comparable. Based on the ROBINS-I tool assessment of the ITC analysis, two domains of "Confounding" and "Bias in selection of the reported result" were rated at "Moderate" risk of bias, and the remaining domains were rated at "Low" risk of bias.

Some outcomes (TTR, TTD, TTNT, and MRD rate) measured in the MajesTEC-1 and MonumenTAL-1 trials and specified in the NICE Final Scope (See Table 7) are

not reported in the ITC analysis results. This may potentially represent selective reporting bias.

Overall, the ITC analysis study was judged to be at Moderate risk of bias. The EAG believes that for this appraisal, the ROBINS-I tool is a more appropriate and relevant tool to use than the modified 27-item Downs and Blacks checklist for non-randomised trials used by the company.

2.2.2 ITC methods

In the ITC analysis, the efficacy and safety evidence for talquetamab (0.8 mg/kg SC every two weeks) versus teclistamab (1.5 mg/kg SC weekly) was informed by IPD sets from the two studies conducted by the company

- MonumenTAL-1 (Cohort C n=154; September 2024 DCO) and
- MajesTEC-1 (All Treated Analysis Set n=165; August 2023 DCO).

In the MonumenTAL-1 trial (on September 2024 DCO), [redacted]/154 [redacted]%) of the study participants did not complete the study, of whom [redacted]%) died, [redacted]%) withdrew consent, [redacted]%) started subsequent anti-cancer therapy, and [redacted]%) was lost to follow-up (CS Table 9). In the MajesTEC-1 trial (on August 2023 DCO), [redacted]%) participants did not complete the study, of whom [redacted]%) died and [redacted]%) withdrew the consent.[13, 22]

2.2.2.1 Selection of endpoints for the ITC analysis

2.2.2.1.1 Efficacy outcomes

The efficacy outcomes measured and assessed in MonumenTAL-1 study for talquetamab were also measured in MajesTEC-1 study for teclistamab (see Table 15). The response endpoints (ORR, CR, VGPR) were defined according to the International Myeloma Working Group (IMWG) criteria.[23]

Table 15: Efficacy outcomes of interest: ITC analysis (CS Appendix B: Section B.1.5)

ITC efficacy outcome	Outcome definition
ORR	The proportion of patients who achieve PR or better according to IMWG criteria (assessed by the IRC) ORR=PR + VGPR + CR +sCR
≥CR	The proportion of participants achieving a CR or better (sCR + CR) as assessed by the IRC according to IMWG criteria ≥CR=sCR + CR
≥VGPR	The proportion of participants achieving VGPR or better as assessed by IRC according to IMWG criteria ≥VGPR=VGPR + CR +sCR

DOR	The time from initial documentation of a PR or better to the date of disease progression according to IMWG criteria, or death due to any cause, whichever occurred first defined
PFS	The time from the date of first dose of study intervention to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurred first
OS	The time from the date of first dose of study intervention to the date of the participant's death, due to any cause
ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR= partial response; IMWG=International Myeloma Working Group; IRC= independent review committee; CR=complete response; sCR=stringent complete response; VGPR=very good partial response; DoR=duration of response	

2.2.2.1.2 Patient reported outcomes (PRO)

The company stated that PROs such as HRQoL from the September 2024 DCO were not available in time for the submission deadline and therefore, were not presented in the CS (CS Section 2.6.8 Patient-reported outcomes). In response to EAG clarification questions (B.11) the company provided PRO HRQoL data (EQ-5D-5L, Patient Global Impression of Severity [PGI-S], and EORTC) in tables and graphs but only for the MonumenTAL-1 trial. The EAG confirm that the ITC analysis did not include the PRO HRQoL data. HRQoL information taken directly from MonumenTAL-1 and MajesTEC-1 were input in the company's economic model.(See Section 3.4.9)

2.2.2.1.3 Safety outcomes (adverse events/reactions)

The company's ITC analysis included the incidence of the following safety outcomes compared between the talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1) arms:

- The most common (≥5%) Grade 3 or 4 treatment-emergent adverse events (TEAEs)
- Adverse events of special interest (AESIs)
  - Cytokine release syndrome (CRS)
  - Neurotoxicity: immune effector cell-associated neurotoxicity syndrome (ICANS)
  - Dysgeusia, weight loss, skin disorders, rash and nail disorders
- Infections

The EAG clinical advisors confirmed that these included AE were appropriate. However, one expert suggested neuropathy is missing. The results of ITC AE are presented in Section 2.2.6.

2.2.2.2 Prognostic covariates chosen for the ITC

The list of prognostic covariates included in the ITC are presented in the CS Table 24 (CS Section 2.10.2 Identification of covariates section and forest plots/CS Figures 8-11 (CS Appendix B. 1.6 section).

The company ran multivariable logistic models (for binary outcomes) and Cox proportional hazards regression models (for time to event data) to gauge the prognostic value of each of the 17 covariates. The company estimated the effects of talquetamab versus teclistamab (OR or HR with 95% CIs) for ORR, DOR, PFS, OS. The regression models included coefficients of the treatment term (talquetamab vs. teclistamab), a covariate term (e.g., female vs. male), and an interaction term between the two, adjusted for the 17 covariates.

The final list of covariates selected by the company was based on several rounds of clinical validation meetings that the Company conducted for another intervention in RRMM with multiple clinical experts in July 2022. The EAG asked for further information regarding the selection and remuneration of these individuals during clarification (CQ A.10). The company stated that these meetings included a validation exercise which was conducted to inform the appraisal of ciltacabtagene autoleucel in RRMM (TA889) which drew on the CARTITUDE-1 trial)[24] with the following justification

"As the patient population in CARTITUDE-1 were patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) receiving 4L+ treatment, the prognostic value assessment performed for CARTITUDE-1 remains relevant [to the population in this appraisal]."

The company claim that the initial list of covariates was further validated by four UK clinical experts consulted during interviews conducted in December 2023 for TA1015[6]. All *a priori* selected and validated covariates (n=17) were measured in both the MonumenTAL-1 and the MajesTEC-1 trials. The EAG clinical advisors confirmed the covariates selected were appropriate for this population.

2.2.2.3 Diagnostic balance of baseline covariates in the ITC analysis

The company assessed the degree of overlap in the distribution of propensity scores between the talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1) patient populations before and after adjustment in the ITC. The company calculated SMDs indicating the between-arm mean difference for each covariate, with an SMD > +/- 0.2 suggesting a substantial difference (i.e., imbalance). This allows for evaluation of the extent to which the weighting adjustment succeeded in balancing out the distribution of baseline covariates between the two different studies of talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1).

The results of these analyses are presented in CS Figures 14-16 (see EAG Section 2.2.3, Table 17 and Figure 2, Figure 3 and Figure 4Figure 4). This diagnostics method allows for the evaluation of how well the weighting adjustment succeeded in

balancing out the distribution of baseline covariates between the two arms of talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1).

2.2.2.4 Data analysis and weighting approaches

The company used the method of inverse probability of treatment weighting (IPTW) (NICE TSD17),[25] to compare the efficacy of talquetamab (0.8 mg/kg SC twice a week; MonumenTAL-1 IPD) versus teclistamab (1.5 mg/kg SC once weekly; MajesTEC-1 IPD) on the *a priori* selected outcomes. This method applies inverse of propensity scores (treatment arm: 1/PS and no treatment arm: 1/1-PS) as weights to create pseudo-population sample(s) with similar baseline covariate distribution, i.e., one that is apparently independent of the treatment assignment.

The propensity scores is a covariate summary defined as an individual's probability of receiving the treatment given the set of baseline covariates (e.g., characteristics/ confounders/prognostic factors). IPTW is more efficient method compared to matching on propensity scores as the latter usually leads to discarded cases which could not be matched. Also, the IPTW uses a single parameter propensity score rather than a number of covariates for the adjustment which is more efficient when there are many covariates relative to the sample size.

Initially, in the IPTW analysis, the propensity scores were estimated in logistic regression models where the dependent variable was the individual probability of receiving talquetamab adjusted for 17 baseline covariates as independent variables.

The company deemed patients treated with talquetamab as the reference population, so they reweighted the MajesTEC-1 IPD using propensity scores to make it comparable to the MonumenTAL-1 IPD with respect to the 17 pre-selected baseline covariates. The company then used the average treatment effect for the treated (ATT) weighting approach and assigned w_1=1 to the MonumenTAL-1 IPD and w_0=PS/1-PS to the MajesTEC-1 IPD.

Weighted logistic and proportional hazards regression models were used to re-estimate relative treatment effects for talquetamab and teclistamab from the MonumenTAL-1 and weighted MajesTEC-1 populations for binary (ORR, CR, VGR) and time-to-event endpoints (KM curves and HR, 95% CI).

The results of these analyses are presented in Section 2.2.3 Table 18 and Table 19 and Figure 5, Figure 6, Figure 7 of the EAG report.

The company also conducted a sensitivity analysis to explore the robustness of the ITC base case estimates of PFS and OS while using alternative weights such as average treatment effect of treatment in teclistamab (ATC), average treatment effect of treatment on the overlap population (ATO), and average treatment effect (ATE)

(see Table 20). Conventional multivariable regression (logistic and Cox) propensity scores -adjusted models and propensity scores matching were also used to estimate talquetamab versus teclistamab effects on PFS and OS. Patients with similar propensity scores were matched using ≤ 0.2 of the standard deviation of the logit of the propensity scores as a matching threshold.

2.2.2.5 Adjustment for switching to subsequent treatment

In the MonumenTAL-1 and MajesTEC-1 trials, some patients who progressed, switched to receive subsequent treatments which are not currently available in routine UK clinical care practice. Therefore, the company conducted a two-stage estimation (TSE) method to remove the effects of switching to subsequent treatment(s) not routinely available in the UK on OS.[26] Full details are provided in CS Section 2.10.4.

Whilst this approach is in line with the approach accepted by NICE in the appraisal for teclistamab (TA1015)[6], the EAG clinical advisors highlight the large variation in subsequent treatments outside and within UK clinical care. The company restricted the ITC analyses for OS (using MonumenTAL-1 to MajesTEC-1 IPD) to treatments available in the UK which are not subject to a managed access agreement (see Figure 1).

- **Stage one adjustment:** the company estimated the magnitude of difference by comparing survival times of patients in MonumenTAL-1 who switched to treatments not routinely used in the UK (n=[redacted]) to those of patients who switched to treatments that are routinely used in the UK (n=[redacted]) who have had at least one subsequent treatment.
    - The company fitted a parametric accelerated failure time (AFT) model with Weibull distribution adjusted for important covariates (refractory status, ISS status, extramedullary disease, cytogenetic risk, number of prior lines, years since diagnosis, age, haemoglobin, LDH, ECOG, time to progression in line prior switching) measured at the new secondary baseline (if available).
    - The model estimated the treatment effect, i.e., an acceleration factor (AF) associated with switching to subsequent treatments not routinely used in the UK. The company noted that the switching to treatments not routinely used in the UK was associated with longer survival times compared to switching to treatments routinely available in the UK.

- **Stage two adjustment:** in stage two, the treatment effect estimated in stage one was used to estimate survival times that would have been observed (if switching had not occurred for patients) who switched to treatments not routinely used in the UK. This method requires a strong assumption of 'no

unmeasured confounding' which the EAG cannot validate.[26] The impact of unmeasured confounding is explored more in Section 2.2.7.

The company stated that their two stage adjustment did not include re-censoring as this would have caused a loss of data, and commented that it is not recommended to be used as the default approach when the objective is to estimate long-term survival extrapolations (CQ A.12).[26] They also rejected the inverse probability of censoring weights (IPCW) approach (CQ A.8) noting that this is a complex method that produces results between the two approaches with- and without re-censoring (CA A.12). In addition, the company rejected the Rank Preserving Structural Failure Time Models (RPSFTM) method as they suggest it would require treatments to be adjusted for in both the talquetamab and teclistamab cohorts (submission Appendix J: Modelling clinical outcomes; page 225).

In summary, the event and censoring rules for PFS and OS for talquetamab in MonumenTAL-1 and teclistamab in MajesTEC-1 were similar and appear appropriate following further clarification from the company (CQ A.9).

2.2.2.5.1 **ITC base case alternative scenarios**

The OS estimates for the company's main ITC (unadjusted for all UK/non-UK subsequent treatments), base case (adjusted for non-UK treatments), and scenarios 1-2 (All-In and All-Out) are presented in

Table 22.

- **Base case scenario**

In the company's base case scenario, OS was adjusted by removing the effects of subsequent treatments not available in UK clinical practice. Teclistamab used as subsequent treatment to talquetamab was allowed in the company modelling, since it is a recommended treatment for reimbursement (see 3.4.10). However, given that talquetamab is not yet available in the UK, its use following teclistamab (see Figure 1) was removed by the company as a subsequent treatment option. Additionally, the use of subsequent teclistamab following teclistamab treatment was removed as an option. The distribution of subsequent therapies before and after adjustment for those not relevant to UK clinical practice are presented later in Table 21.

The company based their subsequent treatment adjustment analyses of OS data on the base case scenario and alternative scenarios:

Two additional scenarios were presented by the company:

- **In scenario 1 (All-Out),** In addition to removing the effects of subsequent treatments not available in UK clinical practice (see Figure 1), subsequent use of teclistamab was removed and the effect of talquetamab received subsequent to teclistamab was also removed from the analysis.

- **In scenario 2 (All-In),** In addition to removing the effects of subsequent treatments not available in UK clinical practice (see Figure 1), subsequent use of talquetamab following teclistamab was permitted, as was subsequent use of teclistamab after talquetamab.

The EAG note that the effect estimates appeared to remain robust across different sensitivity analyses using alternative weighting approaches and adjustment methods (PS matching, PS-based regression), including adjustment for effects of switching to subsequent treatment. However, the EAG have concerns about the overall results of the ITC, this uncertainty is explored in the EAG additional analysis in Section 3.4.6.

The distribution of subsequent therapies for scenarios 1 and 2 are presented in the CS Appendix M.

2.2.3 ITC Results: Prognostic strength of covariates

The regression model results for the potential 17 prognostic covariates are provided in Table 16 (see also forest plots in the CS Appendix B, and B. 1.6 section; CS Figures 8-11). The results indicated that patients with extramedullary disease (EMD), higher ISS stages, or male gender had a [redacted] ORR relative to baseline. In particular, the presence of EMD, a higher number of prior lines, lower haemoglobin, and non-

IgG MM type were found to be associated with [redacted] PFS and OS outcomes relative to baseline.

Table 16: Prognostic covariates for the ITC ranked (adapted from CS Table 24, CS forest plots/Figures 8-11 from Appendix B. 1.6 section).

Baseline prognostic factor [identified and validated based on CARTITUDE-1 trial data (TA889)][24]	Results of multivariable regression [based on IPDs from MonumenTAL-1 and MajesTEC-1]
Priority	**[Outcome] point estimate (95% CI) relative to baseline for talquetamab and teclistamab**
Refractory status (penta vs. double)	[redacted]
Cytogenetic profile (high vs. standard)	[redacted]
ISS stage (III vs. I)	[redacted]
Time to progress on last regimen (≥3 mo vs. <3 mo)	[redacted]
Extramedullary plasmacytoma (No vs. Yes)	[redacted]
Non-priority	
Number of prior LOTs (4+ vs. ≤4)	[redacted]
Years since MM diagnosis (≥6 years vs. <6 years)	[redacted]
Age (<65 vs. 65+)	[redacted]
Haemoglobin (12+ vs. <12)	[redacted]
LDH levels (≥280 vs. <280)	[redacted]
Prior stem cell transplant (No vs. Yes)	[redacted]
ECOG Performance Status (1+ vs. 0)	[redacted]
Race (Other/not reported vs. White)	[redacted]
Sex (Female vs. Male)	[redacted]
Type of MM (non IgG vs. IgG)	[redacted]
Creatinine levels (90+ vs. <60)	[redacted]
Average duration of prior LOTs (≥15 mo vs. <10 mo)	[redacted]

ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System; ITC=indirect treatment comparison; LDH=lactate dehydrogenase; LOT=line of treatment; MM=multiple myeloma; NS=statistically not significant; SS=statistically significant; CI=confidence interval; mo=months; EMD; extramedullary plasmacytoma; HR: hazard ratio; OR=odds ratio; DoR=duration of response; ORR=overall response rate; PFS=progression free survival; OS=overall survival

2.2.4 ITC Results: diagnostic balance of covariates

Prior to adjustment, 15 of the 17 prognostic variables had SMDs within a [redacted] threshold. Only two prognostic covariates (ISS, EMD) were imbalanced (SMDs>[0.2]) between the two arms (see Table 17 and Figure 2).

Following the ATT adjustment, the two trials were well balanced with respect to all 17 prognostic variables, with an SMD [redacted] in all cases, see Table 17 (and Figure 2, Figure 3, Figure 4). The observation of the distribution of PSs after ATT weighting for patients in MonumenTAL-1 and MajesTEC-1 in Figure 4 did not reveal any major skewness or outlier PSs (PS > 0.9 or PS <0.1).In MonumenTAL-1 IPD, only less than [redacted] of the study population had PS close to [redacted].

The EAG consider that there was reasonable degree of overlap between the two trial IPDs and the adjustment process plausibly balanced the baseline characteristics between the two data sets.

Table 17: The baseline covariates in MonumenTAL-1 (talquetamab) and MajesTEC-1 (teclistamab) before and after ITC adjustment [adapted from CS Table 25].

	Before adjustment			After adjustment	
	Talquetamab 0.8 mg/kg Q2W	Teclistamab 1.5 mg/kg SC Q1W	SMD	Teclistamab 1.5 mg/kg SC Q1W	SMD
Sample size	N=154	N=165		N=165	
Refractory status, n (%)					
≤ Double refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triple refractory	[redacted]	[redacted]		[redacted]	
Quad refractory	[redacted]	[redacted]		[redacted]	
≥ Penta refractory	[redacted]	[redacted]		[redacted]	
ISS					
I	69 (44.8)	[redacted]	[redacted]	[redacted]	[redacted]
II	48 (31.2)	[redacted]		[redacted]	
III	37 (24)	[redacted]		[redacted]	
Time to progression on prior therapy					
<3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]		[redacted]	
Number of prior LOTs, n (%)					
≤4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]		[redacted]	
ECOG performance status, n (%)					
0	58 (37.7)	55 (33.3)	[redacted]	[redacted]	[redacted]
1+	96 (62.3)	110 (667)		[redacted]	
Age, n (%)					
<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]		[redacted]	
Gender, n (%)					
Male	90 (58.4)	96 (58.2)	[redacted]	[redacted]	[redacted]
Female	64 (41.6)	69 (41.8)		[redacted]	
Prior autologous stem cell transplantation, n (%)					
Yes	121 (78.6)	135 (81.8)	[redacted]	[redacted]	[redacted]
No	33 (21.4)	30 (18.2)		[redacted]	
Time (years) since diagnosis, n (%)					
<6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 years	[redacted]	[redacted]		[redacted]	
Average duration of prior lines of therapy (months), n (%)					
<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 to 14	[redacted]	[redacted]		[redacted]	

≥15	[redacted]	[redacted]		[redacted]	
Haemoglobin, n (%)					
<12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12+	[redacted]	[redacted]		[redacted]	
LDH, n (%)					
<280	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>280	[redacted]	[redacted]		[redacted]	
Creatinine clearance, n (%)					
<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-<90	[redacted]	[redacted]		[redacted]	
90+	[redacted]	[redacted]		[redacted]	
MM type, n (%)					
IgG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-IgG	[redacted]	[redacted]		[redacted]	
Race, n (%)					
White	126 (81.8)	134 (81.2)	[redacted]	[redacted]	[redacted]
Other/not reported	28 (18.2)	31 (18.8)		[redacted]	
Cytogenetic risk, n (%)					
Standard risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]		[redacted]	
Missing	[redacted]	[redacted]		[redacted]	
EMD, n (%)					
Yes	41 (26.6)	28 (17.0)	[redacted]	[redacted]	[redacted]
No	113 (73.4)	137 (83.0)		[redacted]	

ASCT=autologous stem cell transplantation; ECOG=Eastern Cooperative Oncology Group; EMD=extramedullary plasmacytoma; IgG=immunoglobulin-G; ISS=International Staging System; LDH=lactate dehydrogenase; LOT=line of treatment; MM=multiple myeloma; SMD=standardised mean difference; Q2W=once every two weeks; QW=once weekly

Figure 2. SMDs between MonumenTAL-1 Cohort C (0.8 mg/kg twice weekly) and MajesTEC-1 cohorts, before and after adjustment [CS Figure 14].

Red triangle (unadjusted means), blue circle (ATT).
ATT=average treatment effect for the treated; TEC=Teclistamab; ECOG=Eastern Cooperative Oncology Group; EMD=extramedullary plasmacytoma; ISS=International Staging System; LDH=lactate dehydrogenase; LOT=line of treatment; MM=multiple myeloma; SMD=standardised mean difference.

Figure 3. Distribution of PSs before weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort [Figure 15, the main submission document].

PS=propensity score

Figure 4. Distribution of PSs after ATT weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort (Figure 16, the main submission document).

ATT=average treatment effect for the treated; PS=propensity score.

In summary, the EAG consider that diagnostic balance of covariates appears reasonable

- the ATT-adjusted distribution of propensity scores demonstrates a good overlap between the compared IPDs of MonumenTAL-1 and MajesTEC-1 trials.
- The visual observation did not reveal major skewness or a high proportion of outliers (PS<0.1 or PS>0.9) in the propensity scores distribution.
- The overlapping diagnostics analysis and lack of outlier propensity scores adds some credibility to the methods used in the company ITC results. However, EAG additional analysis questions the results of the company adjustment results (see Section 3.4.6).

2.2.5 ITC Results: clinical efficacy

2.2.5.1.1 Missing data

All patients included in the ITC analysis had outcome data reported, and no patients were excluded from the analysis based on missing data. Efficacy analyses included all 165 participants in the All Treated Analysis Set of the MajesTEC-1 IPD and all [redacted] patients in MonumenTAL-1 trial IPD.

- For MonumenTAL-1 Cohort C, no data imputation was performed and a separate category "Missing" was created to describe the proportion of missing values (0.6% lost to follow-up). The EAG note that no reasons for this were provided for this data missingness (see risk of bias assessment for MonumenTAL-1 in Section 2.1.3.1.2). The proportion of missing data for cytogenetic profile was about [redacted]% however, however no imputation was performed for these data and instead, 'missing' was added as a categorical variable.
- The EAG consider it unlikely that the missing values biased the company ITC effect estimates noticeably.
- For MajesTEC-1, missing data was imputed for the following variables: ISS stage ([redacted]%), years since multiple myeloma diagnosis ([redacted]%), time to progression on last regimen ([redacted]%), and average duration of prior lines ([redacted]%) and for cytogenetic profile the proportion of imputed missing data was greater ([redacted]%), ([redacted]% withdrew from the study).

2.2.5.1.2 Response outcomes

The results of the ATT adjusted ITC analysis are presented in Table 18.

Results indicate that patients in the talquetamab arm had a significantly improved ORR compared to patients in the teclistamab arm (RR=[redacted]). In contrast, there was no statistically significant difference between talquetamab and teclistamab in the proportion of patients achieving ≥CR (RR=[redacted]) or ≥VGPR (RR=[redacted]).

Table 18: Response rates for talquetamab and teclistamab before and after ATT weighting [adapted from CS Table 28].

Response outcome [Tal vs. Tec]	Before ATT weighting (observed)		After ATT weighting (adjusted)	
	MonumenTAL-1 Tal 0.8 mg/kg every two weeks	MajesTEC-1 Tec 1.5 mg/kg weekly	MonumenTAL-1 Tal 0.8 mg/kg every two weeks	MajesTEC-1 Tec 1.5 mg/kg weekly
ORR				
(%)	69.5	63.0	69.5	[redacted]

RR (95% CI); p-value	[redacted]		[redacted]	
≥VGPR				
(%)	59.1	59.4	59.1	[redacted]
RR (95% CI); p-value	[redacted]		[redacted]	
≥CR				
(%)	40.3	46.1	40.3	[redacted]
RR (95% CI); p-value	[redacted]		[redacted]	

ATT=average treatment effect for the treated population; CI=confidence interval; CR=complete response; ITC=indirect treatment comparison; ORR=overall response rate; RR=relative risk; VPGR: very good partial response; Tal talquetamab; Tec=teclistamab; Q2W=once every two weeks; QW=once weekly

2.2.5.1.3 Time to event outcomes

The Kaplan-Meier (KM) curve for DOR (time from achieving ≥ PR to the date of disease progression or all-cause death, whichever occurred first) in 107 responders in talquetamab, alongside the unadjusted ([redacted] responders) and ATT-adjusted ([redacted] responders) KM curves for teclistamab are presented in Figure 5, and the HR 95% CI estimates of the DOR treatment effect for talquetamab versus teclistamab before and after adjustment are presented in Table 19.

The median DOR for talquetamab ([redacted] months; 95% CI: [redacted]) was shorter compared to the ATT-adjusted teclistamab ([redacted] months; 95% CI: [redacted], [redacted]). According to the ATT-adjusted ITC results (Table 19), the risk to disease progression or death in the responder patients was [redacted] different between talquetamab and teclistamab (HR=[redacted]).

Figure 5. DoR KM curves for talquetamab and teclistamab (before and after ATT weighting) [CS Figure 18].

ATT=average treatment effect for the treated; CI=confidence interval; DoR=duration of response; IRC=independent review committee; KM=Kaplan-Meier; NE=not estimable.

The KM curve for PFS in talquetamab and ATT-adjusted KM curves for teclistamab are presented in Figure 6, and the HR 95% CI estimates of the PFS treatment effect for talquetamab versus teclistamab before and after adjustment are presented in Table 19.

The KM PFS curves suggested comparable efficacy of talquetamab (median time: [redacted] months, 95% CI: [redacted]) versus ATT-adjusted teclistamab (median time: [redacted] months, 95% CI: [redacted]). According to the ATT-adjusted ITC results, the risk to disease progression or death in all patients was [redacted] different between talquetamab and teclistamab (HR=[redacted]95% CI:[redacted]).

Figure 6. PFS KM curves for talquetamab (before and after ATT weighting) and teclistamab [CS Figure 19].

ATT=average treatment effect for the treated; CI=confidence interval; IRC=independent review committee; KM=Kaplan-Meier; PFS=progression-free survival.

The OS KM curves presented in Figure 7 indicate that patients receiving talquetamab experienced [redacted] median time to death (not estimable, 95% CI: not estimable, not estimable) than patients in ATT-adjusted teclistamab ([redacted] 95% CI: [redacted]) after the median follow-up of 31.2 months and 30.4 months, respectively.

According to the ATT-adjusted ITC results shown in Table 19, patients receiving talquetamab experienced a [redacted] in the risk of death compared to patients receiving teclistamab (HR=[redacted]95% CI: [redacted]).

Figure 7. OS KM curves for talquetamab and teclistamab (before and after ATT weighting) [CS Figure 20].

ATT=average treatment effect for the treated; CI=confidence interval; IRC=independent review committee; KM=Kaplan-Meier; OS=overall survival.

Table 19: Time to events (DOR, PFS, and OS) of the ITC between talquetamab and teclistamab (before and after ATT weighting) [adapted from CS Tables 29-31].

Response outcome	Before ATT weighting (unadjusted ITC)	After ATT weighting (adjusted ITC)=main ITC
DOR [Tal vs. Tec]		
HR (95% CI); p-value	[redacted]	[redacted]
PFS [Tal vs. Tec]		
HR (95% CI); p-value	[redacted]	[redacted]
OS [Tal vs. Tec]		
HR (95% CI); p-value	[redacted]	[redacted]

ATT=average treatment effect for the treated population; CI=confidence interval; ITC=indirect treatment comparison; HR=hazard risk; Tal talquetamab; Tec=teclistamab; Q2W=once every two weeks; QW=once weekly; DOR=duration of response; PFS=progression free survival; OS=overall survival

2.2.5.1.4 Sensitivity analysis: alternative IPTW weights, PS-regression/matching, and dosing

The sensitivity analysis results for PFS and OS exploring alternative IPTW weightings (e.g., Average effect of treatment in control group [ATC], Average treatment effect [ATE], Average treatment effect on the overlap population [ATO]) and different PS-based ITC methods (i.e., multivariate regression, PS matching) for the base case scenario model are presented in Table 20.

The EAG note that the OS and PFS results (adjusted HRs and 95% CIs) across these approaches appear **comparable in terms of drawing consistent conclusions regarding the efficacy of talquetamab versus teclistamab** in relation to PFS and OS. However, we recognise an unexpected difference in magnitude of OS compared with PFS across all comparisons. See Section 2.2.7 for further EAG comment.

Similar to the main ATT-adjusted ITC analysis, patients receiving talquetamab experienced at least [redacted] statistically significant reduced risk of death compared to patients receiving teclistamab.

Table 20: Base case sensitivity analysis of PFS and OS based on alternative IPTW weightings (ATT, ATC, ATO) adjusted for 17 covariates [CS Table 36]

Comparison	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
Weighting				
ATT (main ITC)	[redacted]	[redacted]	[redacted]	[redacted]
ATC	[redacted]	[redacted]	[redacted]	[redacted]
ATO	[redacted]	[redacted]	[redacted]	[redacted]
ATE	[redacted]	[redacted]	[redacted]	[redacted]
Multivariate regression	[redacted]	[redacted]	[redacted]	[redacted]
PS matching	[redacted]	[redacted]	[redacted]	[redacted]

ATC=average treatment effect for the control; ATE=average treatment effect; ATT=average treatment effect for the treated population; ATO=treatment effect on the overlap population; CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; OS=overall survival; PFS=progression-free survival

2.2.5.1.5 OS adjusted for the effects of switching to subsequent treatments not available in the UK

In the MonumenTAL-1 and MajesTEC-1 studies, [redacted] and [redacted] patients respectively, switched to receive subsequent treatments. Of the [redacted] patients in the MonumenTAL-1

trial, [redacted] received subsequent treatments which are routinely available in the UK and [redacted] received subsequent treatments not routinely available in the UK (see Figure 1 for an overview of UK treatments).

The distribution of subsequent therapies for patients in MonumenTAL-1 and MajesTEC-1 before and after removing the effects of subsequent treatments not available in the UK in the base case scenario is provided in Table 21 and the CS Appendix M. Corresponding KM plots are provided in Figure 8.

Table 21: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, before and after adjustment for subsequent treatments not relevant to UK clinical practice [adapted from CS Tables 26-27].

Patients receiving subsequent therapy (%)	Before subsequent treatment adjustment		After adjustment (re-weighting) for subsequent treatment (Base case scenario)	
	Talquetamab (MonumenTAL-1; Cohort C) N=[redacted][a]	Teclistamab (MajesTEC-1) N=[redacted][b]	Talquetamab (MonumenTAL-1; Cohort C)[c]	Teclistamab (MajesTEC-1)[c]
UK relevant subsequent treatments				
Bendamustine-based regimens	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide-based regimens	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide-based regimens	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan-based regimens	[redacted]	[redacted]	[redacted]	[redacted]
Selinexor	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide monotherapy	[redacted]	-	[redacted]	-
Methylprednisolone monotherapy	[redacted]	-	[redacted]	-
Teclistamab monotherapy	[redacted]	-	[redacted]	
Cytarabine based	-	[redacted]	-	-
Doxorubicin based	-	[redacted]	-	[redacted]
Thalidomide-based	-	[redacted]	-	-
Non-UK relevant subsequent treatments[c]				
Belantamab-based regimens	[redacted]	[redacted]		

Bendamustine-based regimens	[redacted]	-	
Bortezomib plus chemotherapy	[redacted]	[redacted]	
CAR-T cell therapies	[redacted]	[redacted]	
Carfilzomib plus chemotherapy	[redacted]	[redacted]	
Daratumumab-based regimens	[redacted]	[redacted]	
Venetoclax	[redacted]	[redacted]	
Investigational antineoplastic drugs	[redacted]	[redacted]	
Cevostamab plus chemotherapy	[redacted]	-	
Ciltacabtagene autoleucel-based regimens	[redacted]	-	
Cyclophosphamide-based regimens	[redacted]	-	
Dexamethasone-based regimens	[redacted]	-	
Elotuzumab [redacted]	-	[redacted]	
Etoposide [redacted]	-	[redacted]	
Melfufen [redacted]	-	[redacted]	
Idecabtagene vicleucel	[redacted]	-	
Linvoseltamab-based regimens	[redacted]	-	
Talquetamab	-	[redacted]	
Teclistamab	-	[redacted]	

[a] The percentage of patients receiving cyclophosphamide-based regimens, bortezomib-based regimens and bendamustine-based regimens represents the percentage of patients receiving both UK-relevant and non-UK relevant forms of each regimen, as presented in CS Table 22.
[b] Total N refers to patients who survived progression who started at least one subsequent on or after progression date
[c] Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%

Figure 8. OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice (base case scenario) [CS Figure 21].

ATT=average treatment effect for the treated population; CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; KM=Kaplan-Meier; NE=not estimable; OS=overall survival; TAL=talquetamab; TEC=teclistamab

The OS estimates for main ITC (unadjusted for all UK/non-UK subsequent treatments), base case (adjusted for non-UK treatments), and scenarios 1-2 (All-In and All-Out) are presented in

Table 22.

Table 22: Summary of OS ITC analyses, including adjustment for subsequent treatments [CS Table 35].

Comparison	Subsequent treatment allowed (Scenario)	OS HR (95% CI)	p-value
Unadjusted ITC (naïve)	All subsequent treatments allowed (including treatment not available in the UK [non-UK])	[redacted]	[redacted]
ATT (main ITC)	All subsequent treatments allowed (including treatment not available in the UK [non-UK])	[redacted]	[redacted]
ATT (main ITC) + subsequent treatment adjustment (effects of treatments not routinely available in the UK [non-UK] removed)	Current UK treatments allowed (effect of Tec post-Tal retained), but effect of Tal post-Tec removed (**Base case for economic model**)	[redacted]	[redacted]
	Current UK treatments allowed, but effects of Tal post-Tec and Tec post-Tal removed (**Scenario 1: 'All-Out'**)	[redacted]	[redacted]
	Current UK treatments allowed plus both effects of Tal post-Tec and Tec post-Tal are retained (**Scenario 2: 'All-In'**)	[redacted]	[redacted]

ATT=average treatment effect for the treated population; CI=confidence interval; HR=hazard rate ratio; ITC=indirect treatment comparison; OS=overall survival; Tal=talquetamab; Tec=teclistamab

The KM curves for Scenario 1-2 OS are provided in the CS Figures 22-23 (pages 108-109). The distribution of subsequent therapies for scenarios 1 and 2 are presented in the CS Appendix M.

In summary, the company conducted sensitivity analysis to explore the robustness of the effect estimates (PFS and OS) across different scenarios of adjustment methods, including multivariable regression, PS matching, and dosing regimens. The results from these sensitivity analyses were similar to those reported in the company base case analysis. The EAG considers the use of alternative weighting approaches (ATT, ATE, ATO), and the use of the two-stage estimation (TSE) approach to remove the effects of switching to subsequent treatment(s) not routinely available in the UK on OS, appears methodologically appropriate. The analysis showed little variation in the OS HR estimates which were consistently in favour of talquetamab over teclistamab.

However, the EAG were unable to reproduce the company analysis due to lack of access to IPD. Therefore, we were unable to resolve uncertainty surrounding the magnitude of OS compared with PFS across all comparisons. See Section 2.2.6 for detailed EAG comment. The ITC results suggest that most of the OS benefit for patients receiving talquetamab must have started to occur in the *post-progression survival (PPS)* period. Moreover, since OS as an outcome considers all-cause mortality, it may be confounded by deaths due to non-cancer causes (e.g., COVD-19), potentially obscuring the true survival benefit of any given treatment.

In summary, the adjustments made in the ITC conduct generates uncertainties in the effect estimates used to inform the economic model. Whilst there appeared to be a good degree of adjustment and balance in the pre-selected baseline covariates between the compared treatment groups, the model choices used in the adjustments may not be appropriate (this is discussed in detail in the EAG additional analysis, see Section 3.4.6)

2.2.6 Naive comparison of the adverse reactions in MonumenTAL-1 and MajesTEC-1: Adverse reactions

The EAG compared adverse event data from both trials and present these in Table 23. Adverse events of special interest (AESIs) were broadly categorised into: BsAb-specific AEs (i.e., CRS and ICANS/neurotoxicity), GPRC5D-specific AEs (e.g., dysgeusia, weight loss, skin disorders, rash and nail disorders), and infections. The proportion of patients with at least one Grade **≥3**TEAE was greater in MajesTEC-1 (teclistamab) versus MonumenTAL-1 (talquetamab) ([redacted] vs. [redacted] which was mostly accounted for by the blood and lymphatic system disorder TEAEs ([redacted] vs. [redacted]

In contrast, more patients with talquetamab than teclistamab experienced the AESIs of any grade: CRS (74.7% vs. [redacted]%), ICANS ([redacted]% vs. [redacted]%), Dysgeusia (72.1% vs. [redacted]%) weight loss ([redacted]% vs. [redacted]%), skin disorders (73.4% vs. [redacted]%), rash (31.2% vs. [redacted]), and nail disorders (54.5 vs.[redacted]). More patients after teclistamab compared to talquetamab experienced infection of any grade ([redacted]% vs. 70.8%), Grade 3/4 ([redacted]% vs. [redacted]%), and infection with fatal outcome ([redacted]vs.[redacted]). Accordingly, the dose modification (delay, reduction, skip) was more frequent in teclistamab compared to talquetamab ([redacted]% vs. [redacted]%).

Table 23: Naïve comparison: Adverse events for talquetamab (MonumenTAL-1; Cohort C; September 2024 DCO) and teclistamab (MajesTEC-1; August 2023 DCO) [adapted from CS Tables 41-49].

Adverse event N (%)	**MonumenTAL-1 Cohort C [N=154]**	**MajesTEC-1 [N=165]**
	Talquetamab (0.8 mg/kg Q2W)	Teclistamab (1.5 mg/kg Q1W)
Most common (≥5%) Grade 3 or 4 TEAEs		
Patients with ≥1 Grade 3 or 4 TEAE	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Anaemia	39 (25.3)	[redacted]
Neutropenia	33 (21.4)	[redacted]

Thrombocytopenia	28 (18.2)	[redacted]
Leukopenia	[redacted]	[redacted]
Metabolism and Nutrition Disorders	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight decreased	9 (5.8)	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Adverse events of special interest (AESI)		
CRS (any grade)	115 (74.7)	[redacted]
Grade 3/4	1 (0.6)	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
ICANS (any grade)	[redacted]	[redacted]
Grade 3/4	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Dysgeusia (any grade)	111 (72.1)	[redacted]
Grade 3/4	0	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Weight loss (any grade)	64 (41.6)	[redacted]
Grade 3/4	9 (5.8)	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Skin disorders (any grade)	113 (73.4)	[redacted]
Grade 3/4	1 (0.6)	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Rash (any grade)	48 (31.2)	[redacted]
Grade 3/4	8 (5.2)	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

Nail disorders (any grade)	84 (54.5)	[redacted]
Grade 3/4	0	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Infections (any grade)	109 (70.8)	[redacted]
Grade 3/4	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

DCO=data cut-off; Q2W=biweekly; Q2W=biweekly; TEAE=treatment-emergent adverse event; AESI=adverse event of special interest; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome
[a] Dose modification includes delays within cycle, dose reduction and dose skipped

Patient mortality data from the MonumenTAL-1 [talquetamab] and MajesTEC-1 [teclistamab] trials are presented in Table 24. The proportion of all-cause deaths was greater for patients in the teclistamab versus talquetamab ([redacted]% vs. [redacted]%). The proportion of patients who died due to disease progression was greater in teclistamab (n=[redacted]/165 [[redacted]%]) versus talquetamab (n=[redacted]/154 [[redacted]%]). Likewise, more patients in teclistamab versus talquetamab arm died due to infection-related causes (n=[redacted]/165 [[redacted]%] vs. n=[redacted]/154 [[redacted]%]) and AE-associated causes (n=[redacted]/165 [[redacted]%] vs. n=[redacted]/154 [[redacted]%]).

Table 24:Total deaths for talquetamab (MonumenTAL-1; Cohort C; September 2024 DCO) and teclistamab (MajesTEC-1; August 2023 DCO) [CS Table 50].

Death N (%)	**MonumenTAL-1 Cohort C [N=154]**	**MajesTEC-1 [N=165]**
	Talquetamab (0.8 mg/kg Q2W)	**Teclistamab (1.5 mg/kg Q1W)**
Total deaths	[redacted] ([redacted]% of all patients)	[redacted] ([redacted]% of all patients)
Deaths due to PD	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died)
Deaths due to AE	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died)
Not study drug related[a]	[redacted] ([redacted]% of those who died or [redacted]% of all AE-related deaths)	[redacted] ([redacted]% of those who died or [redacted]% of all AE-related deaths)
Study drug related[a]	[redacted]	[redacted] ([redacted]% of those who died)
Infection related deaths	[redacted] ([redacted]% of those who died)	[redacted] ([redacted]% of those who died, or [redacted]% of all AE-related deaths)
Non-infection AE deaths	[redacted] ([redacted]% of those who died)[b]	[redacted] ([redacted]% of those who died)[c]
Other	[redacted] ([redacted]% of those who died)[d]	[redacted] ([redacted]% of those who died)[e]

AE=adverse event; DCO=data cut-off; PD=progressive disease; Q2W=biweekly
[a]Related if assessed by the investigator as possibly, probably, or very likely related to study agent

[b]Causes of non-infection AE deaths for MonumenTAL-1 Cohort C include the following events: [redacted]

[c]Causes of non-infection AE deaths for MajesTEC-1 include the following events: [redacted]

[d]Other category causes of death for MonumenTAL-1 Cohort C include the following events: [redacted]

[e]Other category causes of death for MajesTEC-1 include the following events: [redacted]

The company state that the risk management of infections in patients receiving anti-B cell maturation antigen (BCMA) therapy (e.g., teclistamab) often relies on treatment with intravenous immunoglobulin (IVIg). This was confirmed by EAG clinical advisors who highlighted that "*IVIG therapy can help prevent infections patients and is used prophylactically in routine NHS care.*" The EAG Advisors shared with us the Clinical Comissiong Policy for the use of therapeutic immunoglobulin in England, which was published in March 2025, after the current appraisal commenced. This policy states that "*therapeutic immunoglobulin is recommended to be available as a routinely commissioned treatment option*" (criteria available in EAG Appendix).

Talquetamab is expected to reduce the need for supportive IVIg when compared to teclistamab. This appears to be supported by the evidence from MonumenTAL-1 and MajesTEC-1 trials suggesting a lower rate of IVIg use in patients after receiving talquetamab versus teclistamab ([redacted]% vs. [redacted]%).[13, 16] The EAG clinical advisors confirmed this assumption. However, the company has not considered the substantial rate of patients who received IVIg in the MajesTEC-1trial, when compared to the NHS practice observed in the UK. This is included for consideration in the EAG preference assumptions in Section 5.3.

The EAG note that in TA1015,[6] the CS for teclistamab (see page 179) Johnson & Johnson suggest that the proportion of patients receiving IVIg in the TA1015 base case economic analysis (and the subsequent costs) was overestimated. See text below taken from TA1015,[6]

"*In the absence of available data on [*immunoglobulin*] Ig usage in TCE RRMM patients in UK clinical practice, the MajesTEC-1 trial was considered the best source of data to inform Ig usage in the economic model, to align with the observed efficacy data. The eligibility criteria for receiving Ig replacement therapy in the MajesTEC-1 trial was less stringent than criteria currently used in UK (as specified by the NHS Clinical Commissioning Group). Indeed, the UK guidance stipulates that patients must have hypogammaglobulinemia and IgG <4g/L, recurrent or severe bacterial*

infection and documented vaccine challenge, to be eligible for Ig to treat their secondary antibody deficiency.

*As such, only a subset of patients receiving Ig in the MajesTEC-1 trial would have been eligible this therapy in UK clinical practice. Therefore, the proportion of patients receiving Ig in the base case economic analysis (and the subsequent costs) is considered an overestimated assumption. This is supported by the fact that [*information redacted in TA1015*] and [*information redacted in TA1015*] of patients are modelled to receive IV and SC Ig, respectively in the base case analysis based on the observed data from the MajesTEC-1 trial. In contrast, when the existing UK restrictions are considered, only [*information redacted in TA1015*] and [*information redacted in TA1015*] of patients would have received IVIg and SCIg in the MajesTEC-1 trial, respectively, although the variation for the use of Ig may have potentially impacted safety and efficacy outcomes."*

Following clinical expert advice, and information presented in TA1015[6] the EAG consider that data IVIg use are likely to be overestimated compared to the practice in the UK.

2.2.6.1.1 Adverse events summary

The ITC results indicate that talquetamab demonstrated comparable (for CRS, AEs of Metabolic/Nutrition disorders System Organ Class/SOC) or a better safety (for total grade 3-4 TEAEs, AEs of Blood/Lymphatic System Disorders SOC, any grade infections, grade 3/4 infections, fatal infections) profile compared to teclistamab.

In contrast, teclistamab compared to talquetamab showed better safety profile for ICANS and GPRC5D-specific AEs (e.g., dysgeusia, weight loss, skin disorders, rash and nail disorders). The GPRC5D-specific AEs are less severe and thus easier to manage their risk. Furthermore, the reduction in grade 3/4 infections associated with talquetamab correlate with a reduced intravenous immunoglobulin (IVIg) use. In MonumenTAL-1, only [redacted]% of patients received IVIg compared to [redacted]% in MajesTEC-1. The use of IVIg is associated with substantial resource burden in the UK and is explored further in Section 3.4.10.2 of the EAG economic critique.

The EAG suggest that given the AE evidence provided in the trials, talquetamab showed a better safety profile compared to teclistamab.

2.2.7 Magnitude of improvement in OS compared to PFS

From the data presented by the company, the effect of distributions of subsequent treatments appeared to have a negligible effect on the OS HR. However, the magnitude of improvement in OS compared to PFS requires further exploration. The EAG considers that the large benefit, i.e., in OS in favor of talquetamab ([redacted]

reduction in death hazard; HR=[redacted]95% CI:[redacted], is in contrast with the PFS result which was similar between the two treatments (HR=[redacted]95% CI: [redacted]). (see EAG Figure 9 and Figure 10, and Section 3.4.6 EAG additional analysis). The EAG clinical advisors confirmed that the difference in OS and PFS appear implausible. Several possible explanations of the differences were provided by the EAG clinical advisors including

- Potentially healthier patient populations in the trials compared to real-world evidence (explored by the EAG in Section 3.4.6 EAG additional analysis and Table 17)
- Unaccounted for differences in infection rates between to two trials (explored by the EAG in Section 2.2.6 and 3.4.9.1 of the economic modelling)
- There were more infection-related deaths in teclistamab versus talquetamab (Table 23 and Table 24 [redacted]% vs. [redacted]%)
- The potential impact of COVID-19 on treatment pathways and data collection during the trials (explored below).

It is not clear to the EAG, whether the magnitude of improvement in OS is attributable solely to the effect of talquetamab or may at least partly be due to some other extraneous factors such as unknown confounding, post-progression informative censoring, or different reasons for switching to subsequent treatments. Therefore, the EAG further investigated the potential causes of the differences in the rate of infection-related deaths.

In TA1015,[6] there were statements pertaining to the excess of mortality due to the COVID-19 outbreak which occurred during the conduct of the MajesTEC-1 study.[13, 20, 27-30] The company highlighted that among the 94 death events observed at the time of data-cut off, 18 were due to COVID, representing nearly [redacted]) of all infection-related deaths in MajesTEC-1.

On page 79 of the TA1015 CS, the company made the following statement:

"*it is important to note that the MajesTEC-1 trial occurred during the height of the COVID-19 pandemic before widespread vaccinations were available – 18 of the 94 OS events in MajesTEC-1 died due to COVID-19. Therefore, it is highly likely that the observed OS data from MajesTEC-1 are conservative and may underestimate the genuine survival benefit offered by teclistamab now that vaccines and treatments against COVID-19 infections are available*"

On page 111 of the same source, the company went further in providing explanations to the excess of mortality:

"*UK clinical experts consulted during the preparation of this submission noted that the safety profile for teclistamab has improved compared to the data presented from MajesTEC-1. This is, in part, due to patients being enrolled in MajesTEC-1 during the peak of the COVID-19 pandemic (see Section B.2.4.1). Only 7.9% of patients had received a COVID-19 vaccine prior to the first dose of teclistamab, and subsequently, a substantial number of patients (18/165) died due to COVID-19. In current UK clinical practice, COVID-19 is effectively managed given the widespread availability of vaccinations, meaning many of the deaths from COVID-19 in MajesTEC-1 would now be preventable and the OS results are likely an underestimation of the true OS that would be observed in UK clinical practice. Further, the impact of COVID-19 excess mortality has been acknowledged by a NICE Committee as a factor that should be taken into account as part of decision making, as noted in their appraisal of the CDF exit submission for DaraBorDex (TA897) for clinical data impacted by the COVID-19 pandemic*".

These statements are useful in helping to explore the magnitude of OS benefit suggested from the company ITC, (see Table 19: Time to events (DOR, PFS, and OS) of the ITC between talquetamab and teclistamab (before and after ATT weighting) [adapted from CS Tables 29-31].) as they suggest that the rate of vaccination coverage due to COVID is a key variable associated with OS. However, the EAG note that rate of vaccination was not chosen as a covariate included in the method to adjust for differences in baseline characteristics between the two trial populations (see Table 16). The EAG consider it highly likely that the results from the company ITC are confounded by differences in terms of coverage of the COVID vaccination.

The EAG was unable to identify any statements in the CS relevant to the excess of mortality due to COVID (as was observed in the MajesTEC-1 trial). The EAG consider this a major risk of confounding and potential rationale to explain the observed results. This increases the EAG uncertainty in the conclusion that can be drawn from the company ITC for OS (and PFS, since death events are accounted for in the definition of PFS events).

Uncertainty remains as to the reasons for the observation of relatively large benefit size in OS for talquetamab compared to no between-treatment group difference observed for other outcomes (CR, VGPR, DoR). The results from the ITC, however, were shown to exhibit robustness of the findings on OS and PFS. Three additional plausible confounders to OS include

- The EAG note that OS could also be biased if the reasons for switching to subsequent treatments were other than disease progression (e.g., intolerance, adverse events, toxicity) and they differed between the talquetamab (MonumenTAL-1 IPD) and teclistamab (MajesTEC-1 IPD) arms. The company suggests that *"the criteria to commence subsequent therapy*

were the same in both MonumenTAL-1 and MajesTEC-1 trials wherein, unless study drug intolerance was demonstrated, patients must have experienced disease progression to commence subsequent treatment" (CQ A.7).

- The observed [redacted] in OS could be explained by the alternative biologic mechanism (different MM cell target and downstream effects) through which talquetamab [redacted] the occurrence of life-threatening infections [redacted] effectively and safely than teclistamab. This statement is supported by the ITC results provided in Table 24 showing in patients treated with teclistamab versus talquetamab [redacted] rates of infection-related deaths ([redacted]% vs. [redacted]%, respectively) and AE-related deaths ([redacted]% vs. [redacted]%, respectively).

- The EAG also adds that the proportion of patients who discontinued the treatment due to disease progression was similar between the two arms (talquetamab [redacted]% vs. teclistamab [redacted]%).[16, 22] It is unclear, if all patients in teclistamab (MajesTEC-1 IPD) who discontinued the main treatment (i.e., teclistamab) because of disease progression received the subsequent treatment.

    - For example, in MonumenTAL-1 IPD, [redacted] of all [redacted] patients who discontinued receiving talquetamab did so due to disease progression.[16] Given the data submitted by the company (CS Table 26), [redacted] patients received the subsequent treatment after their disease progression. Therefore, the EAG suspect that all [redacted] patients who discontinued talquetamab due to disease progression (plus [redacted] more who may have discontinued talquetamab due to other reason(s)) did receive the subsequent treatment.
    - This differs in the MajesTEC-1 IPD where from a total of 165 patients, [redacted] discontinued teclistamab due to all reasons, of whom [redacted] patients discontinued teclistamab due to disease progression.[22] However, the EAG notes that of these [redacted] patients who discontinued teclistamab due to progression, only [redacted] received subsequent treatment (CS Table [redacted]). This leaves [redacted] patients who discontinued teclistamab due to disease progression who also did not receive the subsequent treatment. If this is the case, the supposed worsened prognosis of this 'untreated' patient group might have overestimated the OS benefit by certain magnitude in favor of the talquetamab arm.

2.2.7.1 Additional analysis conducted by the EAG: ITC hazard ratios (talquetamab versus teclistamab) in context

The ITC hazard ratios used in modelling OS and PFS may be compared with those reported in other studies of comparisons of treatments for RRMM.

The EAG identified two studies that investigated this relationship, Cartier et al.[31] and Etekal et al.[32] In these studies, the authors undertook linear regression analysis of RCTs / phase III studies that reported hazard ratios for both OS and PFS between compared treatments; the authors presented regression analyses in Figures depicting the relationship between OS HR and PFS HR.

The EAG digitised these published figures, and the results are presented in Figure 9 and Figure 10.

Figure 9: Digitised reconstruction of Cartier et al., regression analysis (square talquetamab, triangle teclistamab)

In the Cartier regression analysis, all studies except one lie within the dashed red regression lines in Figure 9. The company submission ITC HR pair for talquetamab versus teclistamab (PFS [redacted], OS [redacted]) is indicated by the black square; it appears to be an outlier relative to the Cartier et al. studies. In TA1015 (teclistamab) HRs for the comparison teclistamab versus Pom-Dex was reported as [redacted] (PFS) and [redacted] (OS) and appears not to be a clear outlier as indicated by the black triangle.

An additional study was identified by the EAG, Etekal et al.[32] This study reported several regression analyses: one for all included studies (n=41), another (n=39)

excluding two studies considered to be outliers and another, perhaps more relevant, for studies of treatments for RRMM (n=16). The association between PFS and OS HRs was reported to be weak for the two former analyses and the authors concluded that PFS was an inappropriate surrogate for OS.

In the case of studies of treatments for RRMM Etekal et al.[32] reported that the correlation between PFS and OS was 0.76 (95%CI: 0.42, 0.91), concluding this indicated a medium association of PFS with OS. When the HR pairs for talquetamab versus teclistamab (black square in Figure 10) and for teclistamab versus Pom-Dex (black diamond in Figure 10) are plotted with the Etekal data. The EAG consider both pairs appear to be outliers particularly that for talquetamab versus teclistamab.

Figure 10: Digitised reconstruction of Etekal et al., regression analysis for treatments of relapsed-refractory MM

In summary, the ITC hazard ratios for OS and PFS for talquetamab appear to be an outlier when compared to previously reported RWE pairs of hazard ratios for MM treatments including treatments for RRMM. This confirms the EAG concerns pertaining to the magnitude of OS benefit for talquetamab relative to teclistamab. The ITC hazard ratio pairs (PFS OS) for teclistamab versus Pom-Dex from TA1015 is more equivocal relative to values from other studies and seemingly a more moderate outsider.

In summary, the EAG considers that the ITC results should be interpreted with caution due to statistically and/or clinically determined uncertainties.

- **The EAG consider that the OS HR for talquetamab compared to teclistamab from the CS ITC is an outlier.**
- **The exploratory analysis of real-world studies (French and German) conducted by the EAG suggests that the results of MonumenTAL-1 versus MajesTEC-1 may overestimate the effectiveness of talquetamab.**

2.3 EAG summary of the company indirect comparison

Although the ITC provided adjusted comparisons of treatments effects (see Section 2.2.5.1.5), the EAG highlight that this was not a head-to-head randomised controlled trial comparing talquetamab and teclistamab. Therefore, confounding is inherently possible and becomes very likely when important covariates are not accounted for, such as COVID vaccination rates.

The clinical benefits of talquetamab compared to teclistamab observed for ORR and OS may have been biased due to confounding arising from unknown or unmeasured covariates which are independently associated with the prognosis of RRMM.

- For example, the 17 *a priori* selected covariates (as potential and actual confounders) were identified and validated on the sample of TCE RRMM patients receiving 4L+ treatment in CARTITUDE-1 trial of ciltacabtagene autoleucel (TA889).[24] Although the prognostic value assessment performed for CARTITUDE-1 remains relevant to the 4L+ TCE RRMM patients in MonumenTAL-1 trial, the same validation of the MonumenTAL-1 IPD might have generated a different set of unmeasured important covariates associated with the RRMM prognosis outcomes.
- Incomplete (missing) confounder data (such as COVID vaccination rates), and covariate data may have led to incomplete adjustment for these variables.
    - For example, about [redacted]% of the patients had missing data for cytogenetic profile, i.e., baseline covariate classified as priority (CS Table 24) which the company stated were not imputed for MonumenTAL-1.

- Regarding the validity of two-stage adjustment for switching to subsequent treatments, two assumptions need to be met 1) the assumption of 'no unmeasured confounding,' 2) and the assumption of 'no time-dependent confounding'. It is not clear to the EAG, if the time period between the disease progression and switching to subsequent treatments was too long. The company response to clarification letter stated (CQ A.12):
    - "*Time of secondary baseline and the time of receipt of non-UK treatment were not differentiated*. *Secondary baseline was defined as the first time a patient received a non-UK relevant subsequent treatment, or the start of the first UK-only relevant subsequent therapy, rather than as disease progression*."

    - This implies that the company adjusted for the covariates measured at the secondary baseline, and it did not collect data on time-dependent covariates post-secondary baseline. Thus, if the period between the secondary baseline and the switch to subsequent treatment was not short enough, time-dependent confounding might have taken place.[26]

- The two-stage adjustment method described (see Section 2.2.2.5) utilised Accelerated Failure Time Weibull distribution model only. The EAG notes that the robustness and uncertainty of the Accelerated Failure parameter was not explored in models with alternative distributions (e.g., LogNormal, log-logistic, Gamma, Gompertz). The EAG has conducted additional analysis presented in Section 3.4.6 to inform the EAG base case. The EAG has conducted additional analysis presented in Section 3.4.6 to inform the EAG base case.

Additional uncertainty in the results stems from the inconsistent observed benefits for talquetamab versus teclistamab across the ITC reported outcomes (See

Table 22). For example, in contrast to the observed differences in ORR and OS in favour of talquetamab versus teclistamab, there were no significant differences between the two treatments for the remaining outcomes of very good partial response [≥VGPR], complete response [≥CR], duration of response [DOR], and PFS.

- Some outcomes (TTR, TTD, TTNT, and MRD rate) measured in MonumenTAL-1 and MajesTEC-1 trials and specified in the NICE Final Scope (Table 7) were not reported in the company ITC analysis. This may be a potential for selective reporting bias.
    - Selecting and reporting only those outcomes with significant differences in favour of the intervention (talquetamab) will overestimate the overall beneficial effect of treatment.

- The ITC did not include the comparative analysis of PRO HRQoL outcomes between the talquetamab and teclistamab arms. Both patients and clinicians consider HRQoL to be a very important aspect of daily life of a patient with RRMM.

2.4 Conclusions of the clinical effectiveness section

The company decision problem largely matched the NICE Final Scope with the addition of one outcome (MRD) and limiting the comparators to teclistamab only (see Table 7).

- The EAG clinical advisors considered teclistamab the most relevant comparison for this appraisal.

The company conducted a reasonable quality SLR. The SLR did not identify any head-to-head trials investigating the efficacy of talquetamab compared to teclistamab.

- The SLR identified and included two single-arm trials, MonumenTAL-1[12, 16, 33] and MajesTEC-1[13, 20, 27-30] which reported safety and efficacy of talquetamab (technology of interest) and teclistamab (the relevant comparator), respectively.
    - MonumenTAL-1[12, 16, 33] and MajesTEC-1 were single-arm trials conducted in the setting of the 4th line of treatment or beyond (4L+) in TCE adult patients with RRMM who progressed on the last treatment received.
    - Although both trials were designed as international multicenter studies, only the comparator trial (MajesTEC-1) included UK patients (n=[redacted]). MonumenTAL-1 recruited no UK patients.

- Both the MonumenTAL-1[12, 16, 33] and MajesTEC-1 studies were rated at low risk of bias by the EAG (See Section 2.2).

MonumenTAL-1 was the registrational trial supporting the licence application for talquetamab and therefore, forms the principal source of effectiveness data for this appraisal.

- MonumenTAL-1 in a multiphase open label single arm study including Phase I (part 1: dose escalation, part 2: dose expansion) and Phase II (part 3: dose expansion). In Phase II (part 3), talquetamab was administered SC at the Recommended Phase 2 Dose (0.4 mg/kg weekly or 0.8 mg/kg every two weeks) confirmed in Phase I (part 2).
- The company selected one (of 3) Cohorts from MonumenTAL-1 for inclusion in this appraisal. (Cohort C n=154; September 2024 DCO). EAG clinical advisors agreed that Cohort C reflected potential NHS future practice.

As the SLR identified no head-to-head trials, the company conducted an adjusted indirect treatment comparison (ITC) analysis to evaluate the comparative efficacy and safety of talquetamab versus teclistamab using IPD from both company owned trials

- The EAG agree that this was an appropriate approach given the limitations of direct evidence available. However, there are uncertainties in the approach to analysis which is considered in EAG additional exploration of parametric model choice, see Section 3.4.6.

- The company's adjusted (ATT-adjusted IPTW-based) ITC analysis was informed by IPD sets from two Cohorts in MonumenTAL-1[12, 16, 33] and MajesTEC-1[13, 20, 27-30]
  - MonumenTAL-1, Cohort C n=154; September 2024 DCO
  - MajesTEC-1, All Treated Analysis Set n=165; August 2023 DCO.
- The adjusted ITC results (base case scenario) suggest significant improvements in the overall response rate (ORR; [redacted] improvement) and OS ([redacted] reduction in the hazard of death) in favour of talquetamab compared to teclistamab.
  - All other ITC outcomes (very good partial response [≥VGPR], complete response [≥CR], duration of response, and progression-free survival), indicated no significant difference between the two treatments.
- The overall ITC methodological conduct generates uncertainties in the effect estimates used to inform the economic model. Whilst there appeared to be a good degree of adjustment and balance in the pre-selected baseline covariates between the compared treatment groups, the model choices used in the adjustments may not be appropriate (this is discussed in detail in the EAG see Section 3.4.6)
- The EAG risk of bias assessment of the ITC analysis study using the ROBINS-I tool[21] was judged to be at Moderate risk of bias, which disagrees

with the company's assessment of risk of bias for MonumenTAL-1 and MajesTEC-1 trials, judged to be at Low risk of bias.

The EAG considered the results of the ITC uncertain and should be interpreted with caution.

- The EAG consider the benefit in OS in favour of talquetamab may have been overestimated if this or other differences were not accounted for in the analyses.
    - Due to lack of access to IPD the EAG were unable to resolve this uncertainly.
- The potential for bias in the ITC effect estimate which inform the company modelling remains due to unmeasured/unknown confounding factors and the uncertainties including
    - Potentially healthier patient populations in the trials (explored via consideration of RWE by the EAG in Section 3.4.7.5)
    - Difference in infection rates between to two trials (explored by the EAG in Section 2.2.7 and Table 41 of the economic modelling)
        - There were more infection-related deaths in teclistamab versus talquetamab (Table 23 and Table 24 [redacted]% vs. [redacted]%)
    - The impact of COVID-19 deaths and vaccination rates on trial results (Section 2.2.7).

Overall, the EAG considers that the results of the company ITC should be interpreted with caution due to statistically and/or clinically determined uncertainties. The EAG cannot be certain that the clinical effectiveness results provide an unbiased estimate of the treatment effect. There are remaining uncertainties regarding the reliability of the clinical effectiveness evidence (see Table 1 EAG Key Issues) which cannot be resolved in this appraisal due to lack of head-to-head trials investigating the efficacy of talquetamab compared to teclistamab.

3 COST EFFECTIVENESS

3.1 EAG comment on company's review of cost-effectiveness evidence

This section focuses on the economic evidence submitted by Johnson & Johnson and, additional information received in response to the EAG's clarification questions. The EAG critically appraised the evidence submitted and examined the company's electronic model. We provide a summary and critique of the company's economic

evidence, including the company's SLR methods, and results (base-case, sensitivity and scenario analyses) as reported in the CS document using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall reporting quality and validity of these analyses. In the subsequent section, where possible, the EAG have addressed the concerns raised in the form of additional analyses undertaken, which concludes with the EAG base-case.

The submission received by the EAG included:

- A systematic review of the economic evidence
- Methods used to undertake the economic analysis, the company's base-case and sensitivity analysis results
- Electronic version of the de novo Markov model built in Microsoft Excel
- Budget impact analysis (not appraised by the EAG).

3.2 EAG comment on company's review of cost-effectiveness evidence

The company undertook SLRs to identify cost-effectiveness, resource use and cost evidence in patients with RRMM. Additionally, an SLR was undertaken to identify studies that reported HRQoL in the same population, also limited to the UK. These are reported in CS Appendices E, F and G respectively.

3.2.1 Search strategies

Full search strategies for the cost-effectiveness and costs/health resource use SLRs are reported in CS Appendix E.1.1, Tables 29-33. The searches for both SLRs were undertaken in December 2024, with a date limit of 20 October 2021. The SLR methods in the company appendix refer to a previous, broader SLR (searches run May 2020, from database inception) and 1st update (searches run Oct 2021), which also sought HRQoL studies (see CS section B.3.1) and was not limited to the UK. Search terms for RRMM were combined with several established search filters for economic studies, to ensure sensitivity. Search terms for RRMM are combined with a sensitive, validated search filter for identifying health state utility studies in Ovid MEDLINE,[34] which is adapted appropriately for use in Embase and CENTRAL.

The EAG concludes that for all SLRs, a good, appropriate range of databases and other sources (including HTA bodies' websites and proceedings of relevant conferences) were searched in December 2024. Included studies of relevant SLRs, meta-analyses and HTAs were also checked for additional relevant primary studies. In total, seven studies were considered relevant for the systematic review, five obtained from the database searches and two from supplementary searches. However, none included an economic evaluation of talquetamab versus teclistamab from a UK perspective and therefore, were not included in the cost-effectiveness analysis.

The EAG concludes that the searches are likely to have captured all relevant studies.

3.2.1.1 SLR methods

The SLR methods of review were largely appropriate, however, the EAG noted that CS Appendix E.2 text and PRISMA (CS Figure 13) contained some errors which were corrected by clarification response to question C.9 (CQ Figure 20). Clarification response C.10 provided lists of publications identified through supplementary searches (congresses, HTA bodies, bibliographies and websites), but excluded at full text review from the cost effectiveness and health-related quality of life SLRs. The EAG notes that these contain the correct numbers of studies.

3.3 Summary and critique of the company's submitted economic evaluation by the EAG

The EAG reviewed Johnson & Johnson's economic evaluation model against the NICE methods guide.[35] A partitioned survival model was developed to assess the cost-effectiveness of talquetamab compared to teclistamab for the treatment of TCE RRMM patients after at least three prior lines of therapy.

3.3.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 25.

Table 25: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Decision problem clearly stated and is in line with the scope developed by NICE.
Comparator(s)	As listed in the scope developed	Several comparators included in the NICE scope, but company only compared talquetamab versus teclistamab.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects that occur following treatment have been considered in the economic analysis.
Perspective on costs	NHS and PSS	Resource use and costs adopts the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-effectiveness analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	40-year time horizon
Synthesis of evidence on health effects	Based on systematic review	Not applicable
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company's preferred measure is in line with the NICE final scope.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L utility data were collected in the MonumenTAL-1 trial. In the model, utilities were treatment-independent, meaning there was a possibility of having different utility values for the same health state.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D-5L health utility values were cross-walked to the EQ-5D-3L using the algorithm described by Hernández-Alava et al.[36]

Element of health technology assessment	Reference case	EAG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has incorporated the QALY weight into the model.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use clearly reported and valued appropriately using current prices and is in line with the NHS and PSS perspective.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate based on a 3.5% per annum for both costs and benefits used.
EQ-5D-5L, EuroQoL five dimension five levels; NHS, National Health Service; NMA, network meta-analysis; PSS, personal social services; QALYs, quality-adjusted life years		

3.4 Model structure

The company used a partitioned survival model (PSM) comprising three health states (pre-progression, progressed disease and dead) to depict disease progression in people with relapse/refractory multiple myeloma and estimated the cost-effectiveness of talquetamab compared teclistamab. The partitioned survival approach uses an area under the curve approach in the overall survival (OS) and progression-free survival (PFS) health states, which is directly taken from parametric curves fitted and extrapolated to the clinical data. Post-progression is derived from the difference in the area under the curve of the two survival health states (OS and PFS).

The model assumes that all people enter the model in the progression-free health state, and over time may remain in that health state, progress or die. Transitions to the dead health state occur from either the progression-free or progressed disease health states. Figure 11 provides an illustrative PSM.

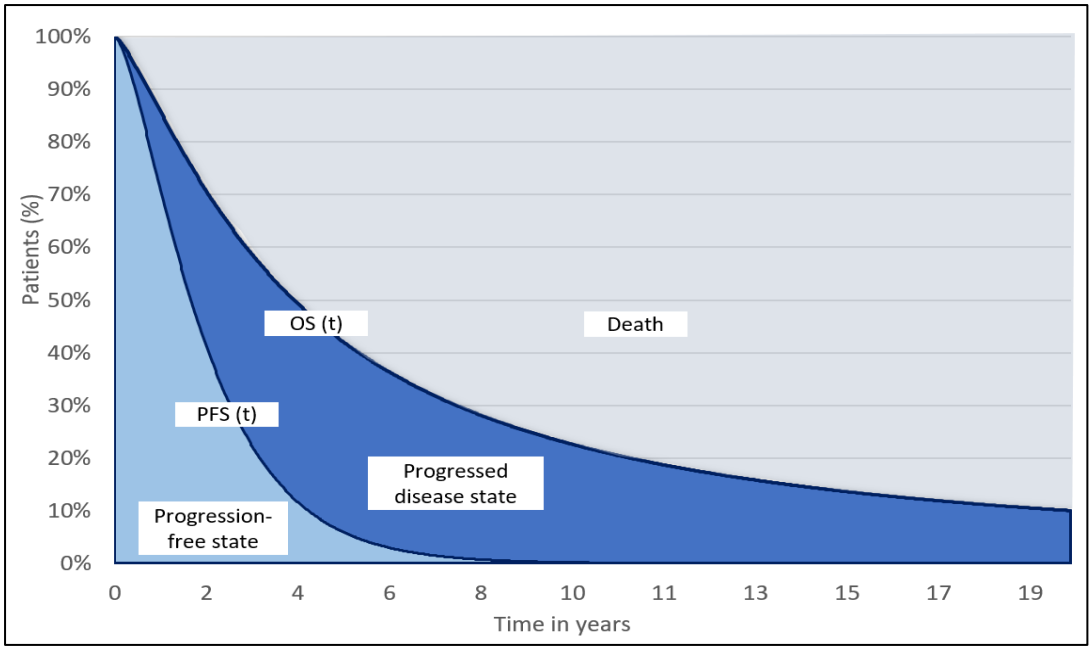

Figure 11: Illustrative partitioned survival model (obtained from Figure 24, CS Document, page 137)

3.4.1 Population

The patient population included in the model reflects Cohort C of the MonumenTAL-1 study: adults with relapsed/refractory multiple myeloma who have received three prior therapies, including IMiD, PI and anti-CD38 mAb and have demonstrated disease progression following their last therapy, which is in line with the decision problem and the licensed indication for talquetamab for use in the UK setting (see Section 2.1.3.1.1.

The baseline characteristics used in the base-case and scenario analysis are presented in Table 26.

Table 26: Baseline characteristics for the model population

Model parameter	Base-case [a]	Scenario analysis [b]
Age (mean), years	[redacted]	[redacted]
Percentage female, %	41.6	[redacted]
Weight (mean), kg	[redacted]	[redacted]
Patient BSA (mean), m^2	[redacted]	[redacted]

[a]MonumenTAL-1 Cohort C (September 2024 DCO)
[b]MajesTEC-1
BSA: body surface area

3.4.2 Interventions, comparators and subsequent treatments

3.4.2.1 Interventions

The cost-effectiveness analysis compared talquetamab against teclistamab. In the model and in line with the license, talquetamab was administered until disease progression or unacceptable toxicity. It was assumed that people received four step-up doses (0.01, 0.06, 0.4 and 0.8mg/kg) in the first week, followed by a maintenance dose of 0.8mg/kg once every two weeks. In the base-case all participants received talquetamab on a dosing regimen of every two weeks. In a scenario analysis, the company assumed that 10% and 90% of people began weekly and every two weeks treatment, respectively. This dosing regimen is in accordance with the license for talquetamab, which also includes weekly administration.

3.4.2.2 Comparators

The comparator included in the economic analysis is teclistamab. In the model and in line with the license, teclistamab was administered until disease progression or unacceptable toxicity. The model assumed that people received two step-up doses: day 1: 0.06mg/kg and at day 3: 0.3mg/kg, followed by a regimen of weekly SC injections (1.5mg/kg). The model assumed that a proportion of people switched from the weekly to the two weekly regimen if they had a complete response or better for at least six months. The company used a Gompertz curve to model the reduced dose frequency starting from 52 weeks.

As confirmed by the EAG clinical experts, treatment with teclistamab is considered the most relevant comparator against talquetamab and, the dosing schedule is in line with UK clinical practice. The approach taken by the company to model a reduced dose frequency of teclistamab is plausible although several additional comparators were included in the NICE scope for this appraisal.

3.4.3 Subsequent treatments

Participants included in the MonumenTAL-1 and MajesTEC-1 trials received subsequent treatments, including those not used in UK clinical practice. The company undertook a two-stage OS adjustment to remove the effects of these subsequent treatments not available in the UK (see Figure 1 Section 1.1.2). Details of the two-stage OS adjustment have been provided in Section 2.2.2.5. The subsequent treatment that participants received in the trials are reported in

Table 27, and Table 28 reports the re-weighting based on the subsequent treatments available in the UK clinical practice.

Table 27: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, before subsequent treatment adjustment

Patients receiving subsequent therapy (%)	Talquetamab (MonumenTAL-1; Cohort C [N=[redacted][a]])	Patients receiving subsequent therapy (%)	Teclistamab (MajesTEC-1 [N=[redacted][b]])
UK relevant subsequent treatments			
Bendamustine-based regimens	[redacted]	Bendamustine based regimens	[redacted]
Bortezomib plus chemotherapy	[redacted]	Bortezomib plus chemotherapy	[redacted]
Cisplatin plus chemotherapy	[redacted]	Cisplatin based regimens	[redacted]
Cyclophosphamide-based regimens	[redacted]	Cyclophosphamide based regimens	[redacted]
Pomalidomide-based regimens	[redacted]	Cytarabine based	[redacted]
Dexamethasone monotherapy	[redacted]	Dexamethasone monotherapy	[redacted]
Melphalan-based regimens	[redacted]	Doxorubicin based	[redacted]
Lenalidomide monotherapy	[redacted]	Melphalan-based regimens	[redacted]
Methylprednisolone monotherapy	[redacted]	Pomalidomide-based regimens	[redacted]
Selinexor	[redacted]	Selinexor	[redacted]
Teclistamab monotherapy	[redacted]	Thalidomide-based	[redacted]
Non-UK relevant subsequent treatments[c]			
Belantamab-based regimens	[redacted]	Belantamab-based regimens	[redacted]
Bendamustine-based regimens	[redacted]	Bortezomib plus chemotherapy	[redacted]
Bortezomib plus chemotherapy	[redacted]	CAR-T cell therapies	[redacted]
CAR-T cell therapies	[redacted]	Carfilzomib plus chemotherapy	[redacted]
Carfilzomib plus chemotherapy	[redacted]	Daratumumab based regimens	[redacted]

Cevostamab plus chemotherapy	[redacted]	Elotuzumab based regimens	[redacted]
Ciltacabtagene autoleucel-based regimens	[redacted]	Etoposide based regimens	[redacted]
Cyclophosphamide-based regimens	[redacted]	Melflufen plus dexamethasone	[redacted]
Daratumumab-based regimens	[redacted]	Pomalidomide based regimens	[redacted]
Dexamethasone-based regimens	[redacted]	Talquetamab	[redacted]
Idecabtagene vicleucel	[redacted]	Teclistamab	[redacted]
Investigational antineoplastic drugs	[redacted]	Venetoclax	[redacted]
Linvoseltamab-based regimens	[redacted]	Other investigational agents[d]	[redacted]
Venetoclax	[redacted]		

Footnotes: [a] The percentage of patients receiving cyclophosphamide-based regimens, bortezomib-based regimens and bendamustine-based regimens represents the percentage of patients receiving both UK-relevant and non-UK relevant forms of each regimen, as presented in CS.
[b] Total N refers to patients who survived progression who started at least one subsequent on or after progression date
[c] This summary of non-UK relevant subsequent treatments only presents treatments received by >1 patient. A table of the full subsequent treatment distribution in MonumenTAL-1 is presented in Appendix L
[d] Other investigational agents include investigational antineoplastic drugs, investigational drug, BFCR 4350A, BFCR 4350A-dexamethasone, CC 92480-dexamethasone, tasquinimod, TAK 573 and monoclonal antibodies
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO); J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).

Table 28: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, after subsequent treatment adjustment (re-weighted to adjust for treatments not relevant to UK clinical practice)

Patients receiving subsequent therapy (%)	Talquetamab (MonumenTAL-1; Cohort C)[a]	Patients receiving subsequent therapy (%)	Teclistamab (MajesTEC-1)[a]
Bendamustine-based regimens	[redacted]	Bendamustine-based regimens	[redacted]
Bortezomib plus chemotherapy	[redacted]	Bortezomib plus chemotherapy	[redacted]
Cisplatin plus chemotherapy	[redacted]	Cisplatin plus chemotherapy	[redacted]
Cyclophosphamide-based regimens	[redacted]	Cyclophosphamide-based regimens	[redacted]

Pomalidomide-based regimens	[redacted]	Pomalidomide-based regimens	[redacted]
Dexamethasone monotherapy	[redacted]	Dexamethasone monotherapy	[redacted]
Melphalan-based regimens	[redacted]	Dexamethasone plus vincristine plus doxorubicin	[redacted]
Lenalidomide monotherapy	[redacted]	Melphalan-based regimens	[redacted]
Methylprednisolone monotherapy	[redacted]	Selinexor	[redacted]
Selinexor monotherapy	[redacted]		
Teclistamab monotherapy	[redacted]		

Footnotes: [a]Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%
Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (September 2024 DCO); J&J IM. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).

At the clarification stage, the EAG requested that the company report the results following a two-stage OS adjustment to exclude the effects of subsequent treatment and to include functionality in the model, so that the EAG could explore the impact to the company's base-case results.

3.4.4 Perspective, time horizon and discounting

The company adopted an NHS and Personal Social Services (PSS) perspective for costs and outcomes, following the NICE reference case. A lifetime time horizon of 40 years was adopted to account for patient outcomes up to age 105 according to the company's trace diagrams. A one-week cycle length was used, aligning with the frequency of clinical events and treatment regimens and a half-cycle correction was applied to health outcomes and costs to account for mid-cycle transitions. Costs and effects were discounted at 3.5% annually, as recommended by the NICE reference case.

EAG summary: The viewpoint of the company's analysis is in line with the NICE recommendations, with all costs included in the analysis reflecting the NHS and PSS perspective. The EAG considers it appropriate to assume a lifetime horizon to capture all costs incurred and benefits accrued for each technology, but this should be capped at 100 years. However, extending the time horizon until people are 105 years is likely to have negligible impact to the company's base-case ICER as most of the cohort would have died.

Despite discounting costs and benefits at the recognised 3.5% per annum, the EAG considers it inappropriate to apply this discounting in the first year. The EAG submitted a clarification question to confirm if the company had indeed discounted within the first year, and they confirmed. However, applying this discount rate in the first year is likely to have negligible impact on the company's base-case ICERs.

The company applied a half-cycle correction to account for mid-cycle transitions. However, the EAG considers that the cycle length is not long enough, to warrant application of this correction.

3.4.5 Overall survival, progression-free survival and time-to-treatment discontinuation

The company owns the IPD for both technologies of this appraisal, talquetamab, and teclistamab. The survival modelling approach for this STA relies on methods used in the previous teclistamab STA, TA1015, which was published in November 2024.[6] The company argues that the survival analysis methodology used in the CS are robust given the recent publication of TA1015 and the alignment of their methods with those accepted by NICE in that appraisal.

While it is true that the survival analysis methodology was previously used in TA1015, the relevance of the underlying survival data from the Majes TEC-1, which informed the survival model for teclistamab, is questionable due to the substantial rate of COVID-related deaths observed in the trial (see Section 2.2.7).

The EAG consider the following issues regarding the company's survival modelling important for consideration by the committee:

- Appropriateness of the log-normal model
- Long-term calibration of chosen survival modelling estimates
- Impact of alternative survival models and the robustness of incremental net health benefit (INHB) across different scenarios
- Appropriateness of the log-normal model
- Appropriateness of the ITC talquetamab versus teclistamab that is applied to the calibrated lognormal model for teclistamab OS to obtain chosen talquetamab model.

The details for the teclistamab modelling are in Section B.3.3.2 of the TA1015 submission.[6] In TA1015, the company fit parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma) to the MajesTEC-1 IPD for OS and time-to-next treatment (TTNT) as a proxy for PFS. The models were fit to the unadjusted data and to adjusted data (after a two-stage adjustment method which removes the effects of subsequent treatments not used in the UK).

For both outcomes after the two-stage adjustment, the log-normal model was the preferred model. However, this calibration raises concerns about the validity of using an AFT-only model like log-normal in a context where proportional hazards assumptions might be more appropriate. Since log-normal does not support a proportional hazards (PH) approach, the justification for applying it within a time-constant HR framework is unclear. While applying a proportional hazards-derived HR to a baseline AFT model like log-normal is conceptually inconsistent, the EAG recognise that this approach is routinely accepted in STA submissions where proportional hazards are supported, and model calibration ensures clinical plausibility. The EAG considers that it is unlikely to materially bias the results in this context, especially given the presumed robustness of the scenario analyses. There is uncertainty regarding the ITC OS HR that is applied to the teclistamab calibrated lognormal model. The company state that resultant talquetamab extrapolations after applying the ITC HRs to the calibrated ATT-weighted teclistamab extrapolations were then capped for GPM.

The EAG have the following considerations to note: a] the patients in MajesTEC-1 were recruited during the COVID 19 pandemic and were not vaccinated against the virus; the teclistamab model to which the HR is applied appears to be unadjusted for the mortality that may be attributable to COVID-19 and therefore may underestimate the true survival of teclistamab recipients; b] published regression analyses of phase 3 studies indicate the company's HR based on two single arm studies may be an outlier. c] recently published real world studies are consistent with the company's likely over-estimation of survival of talquetamab recipients and underestimation of survival of teclistamab recipients.

It is possible that a different model conforming to the use of the PH assumption would naturally align better with expert predictions without requiring calibration. Additionally, the choice to use a single model across OS, PFS, and TTD needs further justification, as these outcomes, while interlinked, frequently do not share identical hazard functions.

3.4.5.1 Long-term calibration of chosen survival modelling estimates

An issue arises that the long-term OS and PFS estimates from the log-normal (and the other models) are misaligned with clinical expert estimates, particularly at 10 and 15 years. For example, the log-normal model estimates 14% survival at 10 years, and 9% at 15 years, while clinical experts estimate 5-15% and 1-5% survival at 10 and 15 years, respectively. To address this misalignment, the company in TA1015 calibrated the log-normal model to force it to match the midpoint of clinical expert estimates at 10 and 15 years. For example, in OS, they adjusted the log-normal model to estimate survival at 10% at 10 years and 3% at 15 years.

However, this calibration was achieved through the application of an attenuation factor after 5 years, which increases the hazard of death in each subsequent cycle to artificially align survival estimates with expert opinion. The justification for this approach remains unclear, particularly given that the log-normal model does not inherently support a proportional hazards framework. Additionally, it is uncertain whether this attenuation method appropriately reflects real-world disease progression or introduces bias into long-term survival estimates.

3.4.5.2 Impact of alternative survival models

The company tested alternative models for talquetamab (see Table 29).

Table 29: Impact of alternative survival models on the incremental net health benefit

Scenario	INHB
Base Case (Log-normal for teclistamab and applying HR to get talquetamab estimates)	0.05
Log-normal individually fit on talquetamab	0.44
Weibull individually fit on talquetamab	0.34
Gamma individually fit on talquetamab	0.18
INHB, incremental net health benefit	

The results demonstrate that using different models affects the cost-effectiveness results, and the Weibull and gamma models give more conservative predictions compared to the individually fit log-normal model.

3.4.6 Overall survival

The company presents Kaplan-Meier analyses for 154 talquetamab recipients from the MonumenTAL-1 and 165 teclistamab recipients from the MajesTEC -1 studies. The talquetamab population was termed Cohort C; this referred to the MonumenTAL-1 study population consisting of patients who had TCE RRMM, who had not received prior T-cell redirecting therapy and had progressed after three previous interventions and who received a company-selected talquetamab dose regimen (2 dose (RP2D) of 0.8mg/kg SC every two weeks). Cohort C contained no UK patients and was followed up for approximately [redacted] months.

Of the 165 patients in the teclistamab TCR group at least [redacted] was from UK and follow-up was approximately [redacted] months. The unadjusted OS hazard ratio between the two arms was reported to be [redacted]). After the ATT adjustments deemed reasonable on clinical advice, the hazard ratio, before subsequent treatment adjustment became [redacted]), a value similar to the indirect treatment comparison (ITC) value after the base case subsequent treatment adjustment of [redacted] applied by the company to the company's teclistamab

OS lognormal model to aid development of the company's base-case talquetamab OS lognormal model.

3.4.6.1 Company's choice of lognormal models

The company has justified the choice of lognormal models on the basis that it was accepted in TA1015 (teclistamab versus POM-DEX).[6]

Given that the company had IPD for both MonumenTAL-1 (talquetamab) and MajesTEC -1 (teclistamab) studies, they are well placed to explore many parametric choices for modelling, and indeed many have been presented within the company's submitted economic model. Nevertheless, despite these options the company has adopted the lognormal approach used in TA1015.

The EAG questions the company's choice and use of lognormal models. This rests on two grounds. Firstly, the company has adopted a PH approach and has applied this to an accelerated failure time (AFT) lognormal model that does not support and is incompatible with the PH approach. Although the EAG agree that a PH approach is justified because the PH assumption is not violated, its application to an AFT model is inappropriate while alternative parametric choices that support PH represent the better choice. In AFT models the relationship between arms is fundamentally different to that in PH models; in AFT models, treatment arms are related in time to survival intervals, in PHs the relationship is between survival values at time intervals. In clarification the company argue for the validity of their approach and EAG are aware of previous STAs where this approach was deemed acceptable. However, the EAG's main objection to the lognormal selection is that alternative models may well fit clinical prediction without the necessity of the extensive adjustment required for lognormal models.

Secondly, when the observed talquetamab OS KM plot is modelled with an unadjusted lognormal model, the resulting extrapolation to the life-time horizon selected for the company's economic model is implausible (red line in Figure 12) [redacted] The EAG opinion is that a lognormal model for talquetamab is unsuitable for extrapolation.

To bring their lognormal model into the realms of plausibility the company adjust the lognormal model by applying clinical advice; the lognormal model is forced to comply with clinical prediction.

Two lognormal models, represented by blue and brown dashed lines in Figure 12, are presented within the economic model. The EAG interpret these as an adjustment to 15 years with a further adjustment to the 40-year horizon. Only after two adjustments is the lognormal model plausible.

Figure 12: EAG generated lognormal models fit to KM plot for talquetamab OS. EAG data extracted from the company submitted economic model

Over the observation period of about 3.6 years the lognormal model delivers the best visual fit to the talquetamab Kaplan-Meir plot; Weibull and gamma models are similar to the lognormal over that observation period (see Figure 13).

Figure 13: EAG generated parametric models to explore fit to talquetamab OS Kaplan-Meier plot.

Note: over the observation period for 154 participants, the lognormal model (green dots) is similar to Weibull and gamma models (solid lines). The influence of the extended flat tail in the KM plot is greater for the lognormal model. (models from the company's economic model).

Therefore, the EAG consider the lognormal model is implausible in extrapolation unless adjusted. In contrast, extrapolated Weibull and gamma models require no adjustment to generate feasible models over the lifetime horizon (see solid lines Figure 14). The other models are over optimistic or, in the case of exponential, have poor fit to the KM plot.

Figure 14: EAG generated parametric models to explore fit to talquetamab Kaplan-Meier plot

Note: on extrapolation the lognormal model (green dots) is implausible and requires adjustment, in contrast Weibull and gamma models (solid lines) generate feasible survival without adjustment (models from the company's economic model).

As shown in the economic model all these parametric models, even the Gompertz model, can be forced into plausibility applying GPM capping (Figure 15).

Figure 15: Parametric models after application of two-stage adjustment procedure

Note: graph from clarification response and also in submitted economic model

The company's base-case talquetamab OS lognormal model is independent of the talquetamab KM plot and of any models based on it. Rather, the talquetamab OS is grounded in the lognormal model for teclistamab. From 5 to 15 years the ITC HR of [redacted] is applied to the teclistamab OS lognormal model; after 15 years the EAG believes the hazard for post-15 year-teclistamab is applied.

This results in a change in the trajectory of the base case survival model seen after 15 years (Figure 16). The ITC HR of [redacted] is applied to the teclistamab OS lognormal model that has been adjusted on clinical advice to equal 10% and 3% survivors at 10 and 15 years respectively. These predictions involve 3-fold and 5-fold extrapolation beyond the 36-month available evidence; they are opinion-driven rather than evidence-based since there is no available evidence beyond 36 months. The application of HR to these values determines the lognormal talquetamab OS at 10 and 15 years and influences the extrapolation to lifetime horizon Figure 16.

Figure 16: EAG generated company base-case lognormal model for talquetamab overall survival together with lognormal models fit to Kaplan-Meier plot for talquetamab OS.

Note: the company's base case Talquetamab model is independent of these curves and of the Talquetamab OS Kaplan-Meier plot.

It is important to realise that the company's base-case talquetamab OS lognormal model is independent of the talquetamab KM plot and of any models based on it. Rather, the talquetamab OS is grounded in the lognormal model for teclistamab. From 5 to 15 years the ITC HR of [redacted] is applied to the teclistamab OS lognormal model; after 15 years the EAG believe the hazard for post-15 year-teclistamab is applied. This results in a change in the trajectory of the base case survival model seen after 15 years (Figure 16). The ITC HR of [redacted] is applied to the teclistamab OS lognormal model that has been adjusted on clinical advice to equal 10% and 3% survivors at 10 and 15 years respectively. These predictions involve 3-fold and 5-fold extrapolation beyond the [redacted]-month available evidence; they are opinion-driven rather than evidence-based since there is no available evidence beyond [redacted] months. The application of HR to these values determines the lognormal talquetamab OS at 10 and 15 years and influences the extrapolation to lifetime horizon Figure 14.

The reliability of the teclistamab data is therefore crucial in judging the reliability of the talquetamab model and any advantage of talquetamab over its comparator. The

EAG have doubts regarding the teclistamab data since it appears not to adjust for the impact of COVID on the survival of the unvaccinated MajesTEC-1 population and may thereby underestimate OS of teclistamab recipients. For similar and additional reasons, the EAG harbours further doubts regarding the ITC HR applied.

3.4.6.2 Alternative models to lognormal for teclistamab OS

Various parametric models presented in the economic model were fit to the observed teclistamab survival KM plot. An unadjusted lognormal model generated some survivors beyond 40 years and is considered implausible (Figure 17); with adjustment by calibration to clinical opinion regarding percentage of patients alive at 10 and 15 years the company base-case lognormal model predicts negligible survivors beyond 32 years. The EAG considers this to be an opinion-led model (Figure 17).

Figure 17: EAG generated unadjusted lognormal fit to teclistamab KM plot (brown line) and company's calibrated lognormal model (red line)

Various parametric models that can support a PH approach were fit to the observed teclistamab KM OS plot; these included Weibull, Gompertz, exponential, gamma and generalised gamma models (presented in the company's submitted economic model). Of note is that the unadjusted lognormal is implausible in extrapolation predicting substantial survivors beyond 40 years.

AIC BIC criteria were not a guide to plausible fit since the teclistamab a Gompertz model scores well on AIC BIC but implausibly predicts approximately 30% survivors beyond the life-time horizon. Of the unadjusted parametric models for teclistamab OS, the Weibull model predicts the closest model to the clinical opinion-led calibration estimates of survival at 10 and 15 years (Table 30). As such it represents the best model of those tested that can support a proportional hazards approach (Figure 18). The lognormal model when unadjusted generates implausible survivors.

Figure 18: EAG parametric models of teclistamab overall survival

A: unadjusted lognormal fit to teclistamab KM plot (brown line) and company's calibrated lognormal model (red line). B: parametric models fit teclistamab OS KM plot: exp = exponential; LN = lognormal; Gomp = Gompertz; ggamma = generalised gamma. All models are unadjusted except the lognormal (brown line)

Table 30: Deviation of unadjusted parametric model OS from calibration predictions

Calibration prediction	Deviation from calibration predictions at 10 and 15 years						
	Weibull	Exponential	Gamma	Generalised gamma	Gompertz	Lognormal	Loglogistic
0.1	0.0454	0.0853	0.0634	-0.0643	-0.1814	-0.0357	-0.0321
0.03	0.0115	0.0282	0.0216	-0.0914	-0.2501	-0.0613	-0.0629

Note: data extracted from the company's economic model. At 40 years the generalised gamma model predicts an overoptimistic 5% survivors.

In summary, the EAG considers the Weibull model a more suitable choice for use in modelling talquetamab survival under a PH approach rather than the company's opinion-led lognormal model that requires opinion-led calibration and is an AFT model incompatible with a proportional hazards approach.

Furthermore, unlike the company base-case teclistamab model, the Weibull model does not require forcing to generate a plausible extrapolation reasonably close to clinical prediction.

In Figure 19 the alternative Weibull "base case" model for talquetamab OS generated under the proportional hazards approach is compared with the company's base case calibrated lognormal model; the Weibull model delivers a more pessimistic result than the company's base case calibrated lognormal model.

Figure 19: Company base-case lognormal model of talquetamab OS (green dots) compared to the Weibull model developed under proportional hazards (PH) approach (red line)

Note: Lognormal models are calibrated. Weibull models are non-calibrated. Model is developed with application of the company's ITC hazard ratio ([redacted]), followed by the company's method for extrapolation beyond 15 years.

Both company base-case and EAG Weibull models predict few survivors beyond 35 years and employ the company's ITC HR of [redacted].

The EAG has doubts about the appropriateness of the company's ITC HR. To gauge the impact of less optimistic values, HRs of 0.6 and 0.7 were applied to the company's teclistamab base-case calibrated lognormal model (Figure 20); less optimistic models of talquetamab survival were obtained and the survival gain of talquetamab over teclistamab substantially diminished.

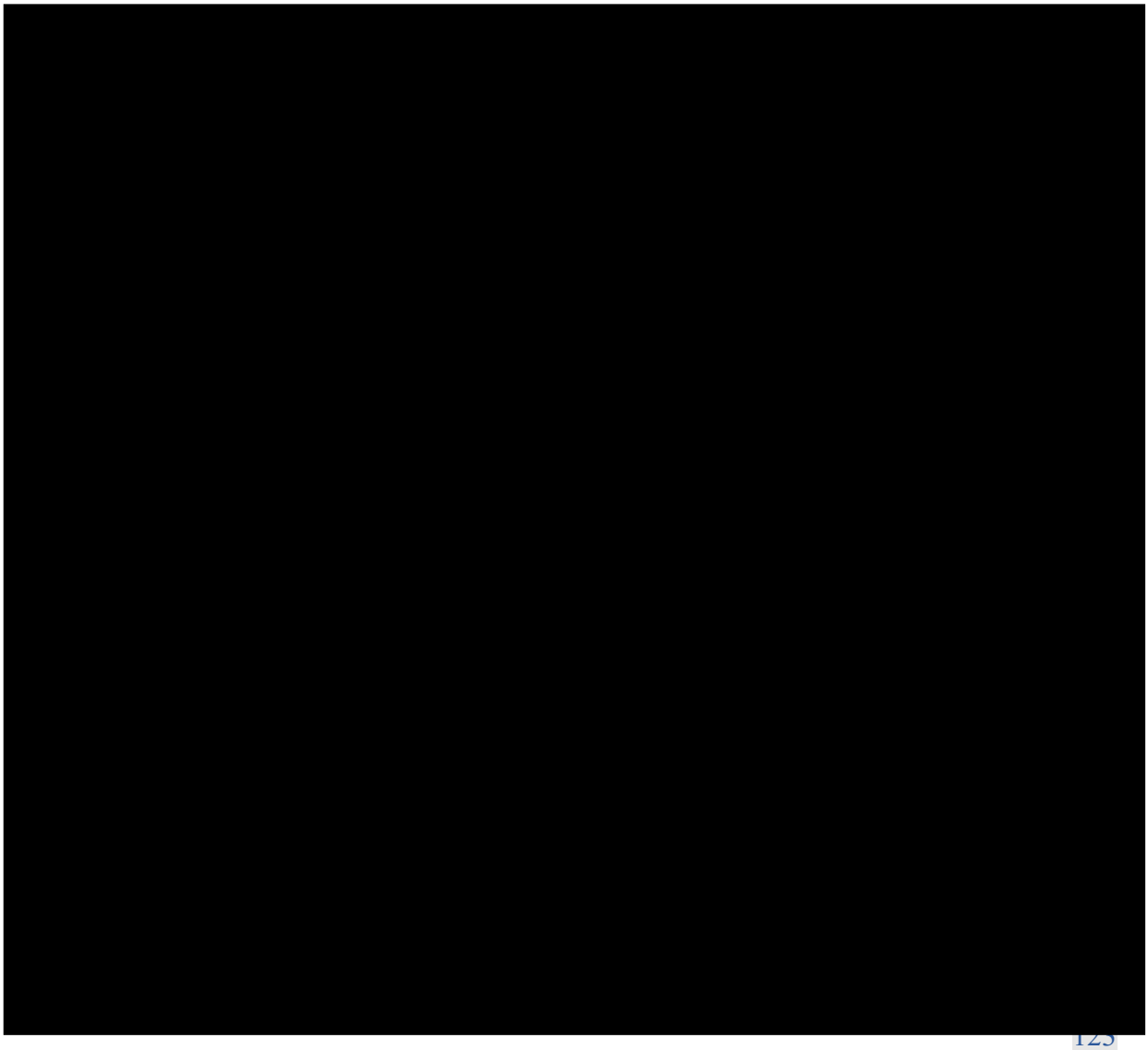

Figure 20: Company lognormal models of talquetamab OS obtained by applying HR [redacted] (green line), 0.6 (red line) or 0.7 (black line) to the lognormal teclistamab model (lower green line).

3.4.7 Progression-free survival talquetamab

Figure 21 shows the “observed” OS and PFS KM plots for talquetamab based on Cohort C and the corresponding plots for teclistamab based on the MajesTEC-1 study. Although PFS is similar between arms (ITC HR = [redacted]), talquetamab OS is superior to teclistamab OS (reported unadjusted HR = [redacted], ATT adjusted (main ITC) HR = [redacted] and base case subsequent treatment adjusted ITC HR =[redacted]). This suggests that even over the short observation period of approximately 36 months there is considerable survival benefit in the talquetamab arm relative to teclistamab arm and that much of this extra benefit occurs after progression (black dashed arrow); in contrast, for teclistamab, post-progression survival benefit is modest relative to pre-progression survival.

Figure 21: Kaplan-Meier PFS and OS plots for talquetamab and teclistamab

Note: Data extracted from the company’s economic model; note: the talquetamab KM plot was not used by the company for modelling talquetamab OS.

To model teclistamab PFS beyond the observation period the company base-case selected a lognormal model that was forced by calibration to fit clinician predictions of the percentage of progressed patients at 10 and 15 years (5% and 1%, respectively (CS Table 54).

Figure 22 shows the resulting calibrated lognormal PFS model (blue line) and the calibration values (black dots). This corresponds to the teclistamab curve shown in CS Figure 30 (that stops at ten years) but Figure 22 extends to 15 years and beyond to 20 years when a negligible percentage remain un-progressed and shows the calibration values used. The implementation of calibration starts at 5 years.

Figure 23 shows the uncalibrated lognormal model (red dash) and the uncalibrated Weibull model (red solid line) as well as the company's base-case calibrated lognormal model (blue line). At 10 and 15 years the uncalibrated Weibull model is almost identical to the calibrated lognormal model and as such fulfils clinical prediction closely. Without calibration the lognormal model seems implausibly optimistic.

Figure 22: The company's calibrated lognormal model of teclistamab PFS
Note: Black dots indicate the calibration values at 10 and 15 years; data taken from the economic model

Figure 23: Lognormal and Weibull models of teclistamab PFS: uncalibrated lognormal model (red dash) and the uncalibrated Weibull model (red solid line) as well as the company's base-case calibrated lognormal model (blue line)
Note: Date obtained from the company's economic model.

The EAG considers the Weibull model preferable: firstly, it fits closely with the clinical predictions whereas the lognormal model is forced to comply with opinion-based calibration. Secondly, the Weibull model supports the proportional hazards approach adopted by the company whereas the lognormal AFT model is less suited.

The deviation of uncalibrated parametric PFS models from clinical calibration predictions at 10 and 15 years is summarised in Table 31. At both calibration times the Weibull model exhibits the least deviation of all models. The lognormal model only fits predictions if it is forced to do so by calibration.

Table 31: Deviation of unadjusted PFS parametric models from calibration predictions

Calibration prediction	Deviation from calibration predictions at 10 and 15 years						
	Weibull	Exponential	lognormal	loglogistic	Gompertz	gamma	Generalised gamma
0.05	0.004855	0.0481	-0.04739	-0.05409	-0.21246	0.027884	-0.12288
0.01	-0.00873	0.009916	-0.057	-0.06692	-0.25246	0.00516	-0.13648

To obtain the base-case PFS model for talquetamab the company applied the ITC hazard ratio of [redacted] (talquetamab versus teclistamab) to the calibrated AFT lognormal PFS model for teclistamab. A superior procedure is provided by applying the [redacted] hazard ratio to the uncalibrated Weibull model. The resulting PFS models are shown in Figure 24. All models are very similar but those based on the Weibull parametric are slightly more pessimistic.

Figure 24: Lognormal and Weibull models of teclistamab PFS

Note: Data taken from the economic model. Talquetamab models (dotted lines) Teclistamab models (solid lines); BLUE = company lognormal models; red = EAG Weibull models.

3.4.7.1 Post-progression treatments and adjustment for their effects

After progression patients become eligible for further treatments and since progression is early in both arms over the observed period of approximately 36 months, there is ample time for patients to receive these treatments. In CS Table 22 the company list 11 post-progression treatments received by Cohort C patients. These eleven are categorised as UK-relevant; CS Table 22 lists 14 post-progression treatments received by Cohort C patients that are classified as non-UK relevant. The treatments listed were received within the September 2024 data cut-off, by which time the observed OS extends to about [redacted] follow-up. Therefore, many of the subsequent treatments were received by Cohort C patients during the observation period and are likely to influence talquetamab OS and post-progression survival. The proportional contributions of talquetamab itself compared to that of subsequent treatments to talquetamab the OS is difficult to estimate.

The company's adjustment for the effect of subsequent treatments upon talquetamab OS involved identifying secondary treatments received and then identifying those likely to be received by UK patients according to clinical opinion.

CS Appendix L lists 85 subsequent treatments received by Cohort C talquetamab recipients who survived progression of their RRMM (n=[redacted]). For the purposes of adjusting for the effect of subsequent treatments, [redacted] treatments were condensed into groups and classified as UK relevant treatments (n=[redacted]) and UK non-relevant treatments (n=[redacted]). The EAG note that the company reweighted the percentage of patients receiving at least one subsequent UK relevant treatment (n=[redacted] treatments) to sum to 100% and provide a similar weight as all treatments. The company call this procedure a two-stage adjustment. (The method is described in detail in Section 2.2.2.5).

In the clinical effectiveness section, the EAG concludes that it is difficult to adjust for the effect of subsequent treatments without knowledge of the depth and duration of their potential survival effect and the number of such treatments received by each surviving post-progression patient. The EAG considers that the reweighting adjustment assumes that the mean effect of UK-relevant treatments is equivalent to that of the non-UK relevant treatments; an assumption that does not have supporting evidence (see Section 2.2.2.5). The subdivision of treatments as UK-relevant or non-relevant represents an opinion-based assumption.

The EAG suggests that the adjustment for secondary treatments likely has an appreciable influence on lognormal base case modelled overall post-progression survival. However, it does not explain the magnitude of OS difference because in all company scenarios: (main ITC (unadjusted for all UK/non-UK subsequent treatments), base case (adjusted for non-UK treatments), and scenarios 1-2 (All-In and All-Out) see Section 2.2.7) there was a clear OS benefit to talquetamab. Potential reasons were discussed in Section 2.2.7. However, the large OS gain for talquetamab over teclistamab is driven by the application of the ITC HR of [redacted] that appears dependent on an underestimate of teclistamab survival (lack of correction for influence of COVID on unvaccinated MajesTEC-1 participants.

The greater post-progression survival benefit from talquetamab versus teclistamab is seen after extrapolation modelling to life-time horizon (see Figure 25). After adjustment for secondary treatments and applying ITC hazard ratios (OS [redacted], PFS [redacted]) the talquetamab base-case OS and PFS curves are as shown in Figure 25. Most survival gain is seen after progression. The teclistamab model is extremely different with most survival gain occurring pre-progression and very little additional benefit thereafter.

Figure 25: Company base-case OS and PFS (green line and brown line) for talquetamab and company base-case OS and PFS (blue line and red line) for teclistamab

Figure 26: Weibull PH model OS and PFS (green line and brown line) for Talquetamab and Weibull PH model OS and PFS (blue line and red line) for Teclistamab

The potential influence of subsequent treatments on post-progression survival is also seen with the EAG proportional hazards Weibull model (see Figure 26). The great difference between talquetamab and teclistamab depends on the large difference in ITC hazard ratios for PFS and OS between treatments.

In summary, the EAG consider that the application of ITC hazard ratios makes post-progression survival dominant for talquetamab and negligible for teclistamab. The company propose that post-progression survival gain is mainly contributed by favourable post-progression effectiveness of talquetamab because they have mitigated the contribution from secondary treatments by appropriate adjustment.

3.4.7.2 Teclistamab and talquetamab real-world studies further EAG exploration

The submission observed OS and PFS Kaplan-Meier plots for talquetamab and for teclistamab may be compared with recently published real-world studies undertaken in jurisdictions with populations probably like UK. These studies are of interest because MonumenTAl-1 did not enrol any patients from the UK and cohort C lacked UK patients.

Three studies were identified by the EAG: two on teclistamab from Germany (Riedhammer, 2024)[37] and from France (Perrot, 2025) on teclistamab[38]; and one on talquetamab from Germany(Frenking, 2025)[39]. Maximum follow up in the studies was 15 months, the German studies included 122[37] and 131 patients[39], the French study 312[38].

The KM plots for OS and for PFS were digitised by the EAG and reconstructed IPD generated using the method of Guyot and colleagues.[40]

Figure 27 shows the resulting teclistamab KM OS (95%CI) plots compared with the company submitted KM over the same time span, the company did not supply 95%CIs.

Figure 27: Teclistamab reconstructed OS KM plots (95% CI) compared with the company submitted teclistamab KM plot. Perrot et al., left (blue line) company (red line) and Riedhammer et al., right, (blue line) company (red line)

Both German and French real-world teclistamab studies exhibit superior OS relative to the company KM (see Figure 27). With 312 patients the Perrot KM has narrower 95% CI; the real-world plots are closely similar except regarding the flat tail in the Riedhammer plot. (Figure 27, right).

Figure 28 shows Riedhammer et al., and Perrot et al., teclistamab reconstructed PFS KM plots (95% CI) compared with the company teclistamab KM plot. In both real-world studies, the PFS plots are close to the company KM.

Figure 28. Riedhammer et al.(lef), and Perrot et al.,(right) teclistamab reconstructed PFS KM plots (95% CI) compared with the company teclistamab KM plot

This result is consistent with that for OS in these studies. There appears to be good correspondence in the submitted PFS and OS KMs compared with the two real world studies. The submitted plots were derived from the previous submission for the cost-effectiveness of teclistamab (using data from MajesTEC-1 study) and therefore, have a different origin to submission OS and PFS K-M plots for talquetamab (cohort C from MonumenTAL-1).

The German real-world study of talquetamab by Frenking[39] presented KM plots for OS and PFS.

compares the reconstructed KM plots (95% CI) with the company submitted KM plots for talquetamab. These suggest superior OS and PFS for the company submission relative to real-world use of talquetamab.

Figure 29. Frenking et al., talquetamab PFS (left) and OS (right) reconstructed KM plots compared with company submission KM plots

In summary the EAG note that the authors of these real-world studies suggest that they are likely to represent the use of these drugs in practice within their jurisdictions (Germany and France) and likely have less narrowly defined populations than seen in the MonumenTAL-1 and MajesTEC-1 trials. As such, relative to real-world usage, they may suggest over optimistic OS and PFS for the submission estimates for talquetamab, but consistency between real world and submitted OS and PFS for teclistamab. Regarding talquetamab misalignment, EAG clinical advisors suggested this may be due to patients enrolled on trial being of poorer health than those in routine care, and RWE studies may more likely represent those patients in the NHS who would receive talquetamab. One clinical advisor suggested that talquetamab is a treatment option where palliative care was previously standard care.

3.4.7.3 ITC hazard ratios (talquetamab versus teclistamab) in context

The ITC hazard ratios (talquetamab vs teclistamab) used in economic modelling of OS and of PFS may be compared with those reported in studies that compared two treatments for multiple myeloma.

The EAG identified two studies that investigated this relationship, Cartier et al.[31] and Etekal et al.[32]

Authors undertook linear regression analysis of RCTs / phase III studies that reported hazard ratios for OS and PFS between compared treatments; the authors

presented regression analyses in Figures depicting the relationship between OS HR and PFS HR. The EAG digitised these published figures, and the results are presented in Figure 30 and Figure 31.

Figure 30: Digitised reconstruction of Cartier et al., regression analysis

In the Cartier et al., regression analysis, all studies except one lie within the dashed red regression lines. The ITC HR pair for talquetamab versus teclistamab (PFS [redacted], OS [redacted]) is indicated by the black square; it appears to be an outlier relative to the Cartier et al. studies. The 95% credible intervals for the ITC [redacted] OS HR spanned the range [redacted] to [redacted]. With an OS HR value between 0.6 and 0.7 (within the ITC 95% credible range) the value ceases to be an outlier according Cartier's regression. The NICE TA1015 HR pair for the comparison teclistamab versus POM-DEX was reported as 0.56 (PFS) and 0.52 (OS) and appears not to be a clear outlier as indicated by the black triangle.

Etekal et al.[32] reported several regression analyses: one for all included studies (n=41), another (n=39) excluding two studies considered to be outliers and another more relevant for studies of treatments for relapsed / refractory MM (n=16). The association between PFS and OS HRs was reported to be weak for the two former analyses and the authors concluded that PFS was an inappropriate surrogate for OS. In the case of studies of treatments for relapsed/refractory MM Etekal et al.[32] reported that the correlation between PFS and OS was 0.76 (95%CI: 0.42, 0.91), concluding this indicated a medium association of PFS with OS. When the HR pairs for talquetamab versus teclistamab (black square) and for teclistamab versus POM-

DEX (black diamond) are plotted with the Etekal et al., both pairs appear to be outliers particularly that for talquetamab versus teclistamab.

Figure 31. Digitised reconstruction of real-world studies

EAG summary, the ITC hazard ratio pair for OS and PFS for talquetamab versus teclistamab appears to be an outliner when compared to previously reported pairs of hazard ratios for MM treatments including treatments for RRMM. The ITC hazard ratio pairs (PFS OS) for teclistamab versus POM-DEX from TA1015 are more equivocal relative to values from other studies and seemingly a moderate outsider. To bring the ITC OS HR into a Cartier non-outlier range (lower dashed red line) would require a HR of approximately 0.60 to 0.70 rather than [redacted], while to bring the ITC OS HR into a Etekal non-outlier range (lower dashed red line) would require a HR of approximately 0.76 rather than [redacted]. These values are within or almost within the 95% CrIs for the ITC OS HR. To fit the regression lines (solid red lines) larger HRs are required.

3.4.7.4 Time-to-treatment discontinuation (TTD)

Figure 32 shows the KM analysis of TTD for Cohort C and teclistamab recipients from the MajesTEC -1 presented in the company's economic model. The KM curves

are similar and right skewed. The median TTD for teclistamab was approximately [redacted]. Only teclistamab data was used for modelling.

Figure 32: Kaplan-Meier analyses of TTD

The company fit a variety of parametric models to the teclistamab KM data. Over the observed period of 36 to 40 months the best visual fit and the lowest AIC BIC values were provided by the lognormal model.

Figure 33 compares the lognormal model (red dots) with five alternative parametric models; most have moderate visual fit to the KM data. The company opted for lognormal modelling of teclistamab and talquetamab TTD.

Figure 33: Lognormal model of Teclistamab TTTD compared to alternative parametric models

Figure 34 compares alternative models with the clinician predictions (red circles) and the uncalibrated lognormal model (green dots). The lognormal model, if not adjusted, predicts patients in treatment beyond 20 years and a few beyond 30 years. The EAG considers this implausible.

To make the lognormal plausible it is necessary to adjust the model by calibration. This was done by making the lognormal extrapolation conform to clinical advisor estimates of the proportion in treatment at ten years (3%) and fifteen years (1%). This adjustment was implemented starting at five years. Gompertz and generalised gamma models are clearly implausible on extrapolation; Weibull and gamma models approach more closely to the clinical predictions without the necessity of calibration that is required by the lognormal model; as such they represent realistic models that do not require calibration.

Figure 34: ***Extrapolated unadjusted parametric models for teclistamab TTD***

The exponential model seems over pessimistic and does not approach the clinical predictions at 10 and 15 years. The deviation of uncalibrated parametric models from clinical prediction is summarised in Table 32, indicating a closer alignment to clinician prediction for gamma and Weibull models than for uncalibrated lognormal model.

Table 32: Deviation of uncalibrated models from clinical prediction

Calibration prediction	Deviation from calibration predictions at 10 and 15 years						
	Weibull	Exponential	Lognormal	Loglogistic	Gompertz	Gamma	Generalised gamma
0.01	0.00536	0.005338	-0.02667	-0.07119	-0.256	-0.25678	-0.3521
0.03	0.01294	0.012245	-0.0409	-0.10513	-0.29	-0.2967	-0.4145

The lognormal model for teclistamab is forced to fit the calibration values at 10 and 15 years. Because a hazard ratio of almost unity ([redacted]) is applied to this model to derive talquetamab TTD the models for each treatment are almost identical (Figure 35).

Figure 35: Uncalibrated lognormal and Weibull teclistamab models compared to calibrated models for teclistamab and talquetamab.

tecNCln = teclistamab uncalibrated lognormal model; tecNCw = teclistamab uncalibrated Weibull model; calyr = calibration values at ten and fifteen years; TALQ = talquetamab calibrated lognormal model. TECL = teclistamab calibrated lognormal model.

Uncalibrated extrapolated Weibull and gamma models provide reasonable fit to clinical prediction; in so doing they have advantage over calibrated lognormal models that require forcing by calibration. Furthermore, they are more suited than lognormal for application of a proportional hazards approach.

Figure 36 compares calibrated lognormal, uncalibrated Weibull and uncalibrated gamma teclistamab TTD models (dots) and talquetamab models (solid lines) generated using a] the company calibrated lognormal procedure; b] the uncalibrated Weibull; and c] the uncalibrated gamma model. Talquetamab models are graphically indistinguishable from teclistamab models because the hazard ratio applied is almost unity. Weibull and gamma models are slightly conservative relative to calibrated lognormal. Over the observed teclistamab KM analysis the Weibull model generates a better visual fit than the gamma model. In view of this and the larger proportion of deaths observed for teclistamab ([redacted] vs. [redacted] talquetamab) and the generally worse adverse event rate for teclistamab seen in Submission Tables 40 to 49, the EAG consider the Weibull models to represent the most suitable option to model TTD.

Figure 36: Comparison of TTD models for teclistamab (dots) and talquetamab (solid lines)

3.4.7.5 Summary of the EAG additional analysis

Given the uncertainty in the company ITC which could not be resolved by head-to-head trial evidence. The EAG conducted several additional analyses to explore the impact of company adjustment and model selection on the results of the ITC and economic modelling. In doing so, the EAG conclude the following

- The company adopted lognormal modelling (for OS, PFS, and TTD) on the assumption that TA1015 procedures were desirable for, and applicable to,

ID5082. The **EAG do not agree that this is a well justified assumption** and believe other options may offer more validity to the cost-effectiveness analysis because:

  - The two STAs are fundamentally different with respect to their comparator to teclistamab.
  - Unlike TA1015, in ID5082 the company owns IPD for both comparators not just one. As such the company can explore many options not just that predicated on the previous TA for teclistamab versus Pom-Dex. The company's economic model does in fact explore many such options, but none of these was adopted for the company's base-case.

- The lognormal models predicated on the TA1015 approach **generate unrealistic OS and PFS for teclistamab.** To generate lognormal models that provided realistic percentages of survivors and of non-progressed patients in extrapolation it was necessary to force or "calibrate" the lognormal models to comply with clinical advisor's predictions at ten and fifteen years. The EAG consider that an evidence base for the opinion-led predictions is difficult to identify or envisage. The EAG have shown that other models, particularly Weibull, fit well to the clinical predictions without being forced by calibration.
  - An evidence base for the opinion-led predictions is difficult to identify or envisage in absence of evidence other than that from MonumenTAL-1 and MajesTEC-1 that is included in the CS.
  - However, in this context, the recent publication of three real-world studies from Germany[37] and France[38] to some extent mitigates this deficiency and suggests that in practice talquetamab may perform less well relative to teclistamab than is suggested by the company's lognormal-based modelling.

- The company adopt a calibration approach to modelling OS and PFS. Calibration is based on clinical opinion defining the proportion of survivors at 10 years and at 15 years in the teclistamab arm (for teclistamab OS these values are 10% and 3% respectively).
  - Calibration has a profound influence on modelling, forcing models to follow a prescribed trajectory.
  - The resulting models consist of three 5-year phases a], b], c], followed by an extended extrapolation from 15 to 40 years. Phase a] extends over years 0 to 5, seven parametric models (with no adjustment) were fit to teclistamab KM plots, these "phase a]" models differ little from one another over this short period. "Phase b]" extends from 5 years to 10 years and all model trajectories are made to converge on the 10-year specified value (10% at 10 years for teclistamab OS), the resulting difference between models diminishes over this period until at 10 years they all reach the same value. "Phase c]" extends from 10 to 15 years and all parametric models are forced to follow almost identical

trajectory to adhere to clinical prediction. Beyond 15 years, lognormal hazards were applied to the teclistamab curves and the model is capped to ensure that the per-cycle hazard of death cannot be lower than the corresponding hazard in the general population. The time horizon extends extending to 40 years over a time that 3.5% discounting has increasing influence, increasing hazard dependent on the individual parametric used.
    - The result of calibration is that differences between the seven parametric models will be minimal. The EAG **does not consider this to represent full exploration** of the available evidence.

- Since OS and PFS talquetamab models are simply derived by applying ITC hazard ratios ([redacted] for OS and [redacted] for PFS) to the teclistamab calibrated models the resulting talquetamab models are calibrated and lack a full exploration of available evidence.

- The company modelled talquetamab OS by applying the ITC HR [redacted] to the selected model for teclistamab (in the company base case this was a calibrated lognormal model). The EAG has **reservations regarding the reliability of the company's ITC HR**. These stem from: a] the apparent lack of adjustment for the impact of COVID 19 on unvaccinated patients recruited to MajesTEC-1 in the development of the ITC; b] regression analyses from phase 3 studies (Cartier et al., and Etekal et al.) suggest that the ITC HR [redacted] for OS is a clear outlier. c] recently published real world studies from France and Germany suggest that the company's OS model for talquetamab patients is too optimistic while that for teclistamab patients is too pessimistic.

- The company adopted a proportional hazards (PH) approach for lognormal models. Lognormal models do not well support PH and application of time-constant hazard ratios to lognormal models is inappropriate; the EAG acknowledge that this approach has been approved for previous STAs but consider it **unnecessary when IPD for both interventions are available**. Models that support the proportional hazards approach are preferable.

- The company's modelling of OS for patients in receipt of talquetamab treatment generated a **large proportion of survival gain accruing after progression** and **after cessation of talquetamab treatment**.
    - This was in contrast to teclistamab where practically no survival benefit accrued after progression; it is problematical to explain this solely based on lingering effectiveness of talquetamab for decades after cessation of talquetamab treatment.

- The modelled post-progression survival for talquetamab treatment could be due to lingering post-treatment effectiveness of talquetamab, as well as to the receipt of effective fifth line subsequent treatments (those reported were received before the cut off September 2024); it may also perhaps be driven by the inappropriate application of the company's time constant ITC OS hazard ratio (talquetamab versus teclistamab, [redacted]) to the AFT lognormal model.
    - The company's efforts to correct for the contribution from subsequent treatments is welcome but essentially opinion- rather than evidence-led; the **resulting base-case model must be associated with considerable uncertainty** that available evidence does not render quantifiable.
    - Furthermore, the ITC hazard ratio pair for OS and PFS employed appears to be an outsider relative to values seen for many previously employed treatments for RRMM in EAG identified RWE studies.

- Recently published real world studies imply that application of talquetamab and teclistamab in real world practice could be substantially less optimistic for talquetamab than the company's submitted model, but in contrast more optimistic for teclistamab than the company's submitted model. These observations **add a further layer of uncertainty** to the economic analysis presented by the company that cannot be resolved completely.

3.4.8 Transition probabilities

The company calculated the proportion of patients in each health state during each cycle using the following methodology: For "pre-progression (on treatment)," the minimum of PFS and TTD was applied, while "pre-progression (off treatment)" was calculated as the difference between PFS and TTD, ensuring non-negative values. For "progressed (on treatment)," the difference between TTD and PFS was used, and for "progressed (off treatment)," the OS minus the maximum of PFS and TTD was considered. Death was modelled as one minus OS.

3.4.9 Health-related quality of life

The utility values were assumed to be treatment independent and thus, based on the health state occupied. The health-state utility values (HSUV) for PFS and PPS were based on information collected using the EQ-5D-5L from participants in the MonumenTAL-1 trial and estimated using mixed models for repeated measures (MMRM). Briefly, EQ-5D-5L questionnaires were completed at baseline, and day 1 of every odd cycle during treatment, then every 16 weeks *'post indication of progressive disease or end of treatment (whichever occurred first).'* Data collected were then mapped onto the EQ-5D-3L value set using the Hernandez-Alava et al. (Hernandez et al., 2017) algorithm. For the PFS health state, separate MMRMs were

fitted to EQ-5D-3L data from patients who remained progression free during each PRO collection time point to estimate mean time-specific progression-free utility values. The overall mean PFS utility was calculated by summing the estimated mean utilities across all time points and dividing by the number of cycles. The mean PPS utility value was estimated using PRO data from patients who progressed and did not include a time-varying component.

In economic model, HSUV were age-adjusted over the model time horizon reflecting the UK general population norms. In Table 33, we report the HSUVs used in the company's base-case model.

Table 33: Summary of utility values for cost-effectiveness analysis (base-case) (CS, document, Table 59)

Health state	Utility value (SE)	Source
PFS	[redacted]	MonumenTAL-1 trial (September 2024 DCO, CS model [lowest AIC])
PPS	[redacted]	
AIC, Akaike information criterion; CS, company submission; DCO, data cutoff; PFS, progression free state; PPS, post-progression state; SE, standard error		

In scenario analyses, the company used utility values based on data obtained from the MajesTEC-1 trial to show the impact on the base-case results. Applying utilities from MajesTEC-1 increases the company's ICER by 6%.

3.4.9.1 Disutilities associated with adverse events

Grade ≥3 treatment effect adverse events, which occurred in at least 5% of participants treated with talquetamab or teclistamab were included in the model as a one-off utility decrement in the first cycle of the model. The base-case adverse event disutilities applied in the model are presented in Table 34 below.

Table 34: Adverse event-related disutilities included in the model, Table 58, CS (pg. 158)

Adverse event	Disutility	Decrement sources
Anaemia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar 2014)
Hypertension	0.0000	TA573 (assume no QoL impact, controlled by medication)
Hypokalaemia	-0.2000	TA510 (based on clinical opinion)
Hypophosphatemia	-0.1500	TA559 (2018)
Infection	-0.1900	TA510 (2018)
Leukopenia	-0.0700	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014)

Lymphopenia	-0.0700	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014)
Neurotoxicity	[redacted]	Assumed to have 0 quality of life
Neutropenia	-0.1500	Brown 2013/Partial Review TA171 (Bacelar 2014)
Pneumonia	-0.1900	Brown 2013/Partial Review TA171 (Bacelar 2014)
Rash	-0.0325	Nafees 2008
Thrombocytopenia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar 2014)
Weight loss	0.0000	Assumed to have 0 disutility in line with TA898
AE, adverse event; QALY, quality adjusted life year		

The EAG notes that including adverse event disutilities in the economic model may lead to double counting because the effect of adverse events on HRQoL is likely to have been captured in the patient-reported outcomes data collected from trial participants, which was used to estimate the HSUVs used in the model. For this reason, the EAG prefers to exclude adverse event-related disutilities in their base-case.

3.4.10 Resources and costs

From the perspective of the NHS and PSS, the company incorporated the following cost categories in the model:

- Drug acquisition costs
- Drug administration costs
- Co-medication costs
- Monitoring costs
- Palliative care costs
- Adverse events costs
- Subsequent treatment costs.

3.4.10.1 Drug acquisition costs

The drug acquisition costs for talquetamab and teclistamab included a confidential patient access scheme discount (PAS), applied to the list prices for both treatment arms and modelled according to the licensed doses as indicated in the Summary of Product Characteristic (SmPC). Data from MonumenTAL-1 and MajesTEC-1 trial showed that [redacted] and [redacted] of talquetamab and teclistamab doses were skipped, respectively. The model also incorporated a reduced dosage frequency for patients undergoing teclistamab, starting from 52 weeks following treatment initiation, modelled using a Gompertz distribution based on data from MajesTEC-1. The dosing regimens for the intervention and comparator as well as the corresponding drug acquisition costs are summarised in Table 35 and Table 36.

Table 35: Summary of drug costs for talquetamab and teclistamab, adapted from Table 60, CS (pg. 161)

Intervention	Dose	Unit	Pack Size	Method of administration	List price per pack (£)	Source
Talquetamab	3/1.5	mg/mL solution	1	SC injection	£326.41	J&J IM. Data on File
	40/1	mg/mL solution	1	SC injection	£4,352.00	J&J IM. Data on File
Teclistamab	30/3	mg/mL solution	1	SC injection	£775.14	J&J IM. Data on File
	153/1.7	mg/mL solution	1	SC injection	£3,952.78	J&J IM. Data on File
SC, subcutaneous						

Table 36: Summary of dosing regimens for front-line treatment included in the model, Table 61, CS (pg. 161)

Intervention	Dosing frequency	Source
Talquetamab (Step Up Dosing for fortnightly regimen)	0.01, 0.06, 0.4 and 0.8 mg/kg 1st week	Talquetamab SmPC
Talquetamab Cohort C (fortnightly dosing)	0.8 mg/kg once every two weeks thereafter	Talquetamab SmPC
Teclistamab (Step Up Dosing)	0.06 and 0.3 mg/kg in Week 1	Teclistamab SmPC
Teclistamab (weekly dosing)	1.5 mg/kg once every week thereafter	Teclistamab SmPC
Teclistamab (fortnightly dosing)	1.5 mg/kg once every two weeks thereafter	Teclistamab SmPC
SmPC, Summary of Product Characteristics		

The company modelled the proportion of vials wasted per patient taking the approach accepted in TA1015.[6] Given there was no data available from UK patients undergoing talquetamab (see Table 7), the company used the mean weight of patients from Cohort C, assuming a normal distribution of weight across all weight bands.

3.4.10.2 Drug administration and co-medication costs

For both the intervention and comparator, drug administration costs comprised a cost for first complex IV infusion, a cost for other IV administration, a cost for each subcutaneous administration, cost for oral drug initiation and a cost associated with

inpatient hospital stays as part of the initial step-up dosing regimen. In the model, patients receiving talquetamab and teclistamab treatment were hospitalised for 8 and 6 days respectively during the step-up dosing stage, in line with the SmPC. The drug administration costs used in the economic model were sourced from the National Schedule of NHS costs and are presented in

Table 37.[41]

Table 37: Drug administration costs, Table 62, CS (pg. 162)

Administration	Cost	Source
Complex first IV infusion	£554.23	National Schedule of NHS Costs 2023-24, SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – Weighted average of Daycase and Regular Day/Night admissions.
Other IV administration	£250.77	National Schedule of NHS Costs 2023-34, SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle – Outpatient.
Each SC administration	£108.90	Cancer Service. National Schedule of NHS Costs 2023-24, N10AF: Specialist Nursing, Cancer Related, Adult, Face to face.
Oral drug initiation	£247.13	National Schedule of NHS Costs 2023-24, SB11Z: Deliver Exclusively Oral Chemotherapy – Outpatient.
IV, intravenous; SC, subcutaneous		

All patients in both treatment arms were co-medicated with Dexamethasone PO 2mg, Paracetamol (acetaminophen) and Diphenhydramine during the step-up dosing schedule. The co-medication dosing regimen and the associated administration costs are presented in Table 38.

Table 38: Co-medication unit costs, adapted from Table 64, CS (pg. 164)

Drug	Dose	Unit	Pack size	Price per pack or unit cost (£)	Dosage per administration	Drug or monitoring cost per admin (£)	Source
Dexamethasone PO 2 mg	2.0	mg	28	1.71	16.0 mg	0.49	BNF 2025
Paracetamol (acetaminophen)	500.0	mg	100	0.79	825.0 mg	0.02	eMIT 2024
Diphenhydramine	25.0	mg	20	3.87	50.0 mg	0.39	MIMS, Nytol
BNF, British National Formulary; eMIT, electronic market information tool; MIMS, monthly index of medical specialities							

3.4.10.3 Monitoring and palliative care costs

The company captured weekly routine monitoring costs (Table 39) in the economic model, with the frequency of tests and visits dependent on progression status and treatment status (for patients in PFS health state). A one-off terminal care cost of £13,314 was applied to the proportion of patients who died in each cycle of the model, based on hospital and social care costs for patients with cancer.[42]

Table 39: Weekly resource use and unit costs for routine follow-up care use by health state, Table 66, CS (pg. 165)

Resource Use	Unit Cost (£)	Frequency per cycle			Source
		PFS (on Tx)	PFS (off Tx)	Post-progression	
Haematologist visit	204.32	0.23	0.08	0.08	NICE TA427[43]
Full blood count	6.95	0.21	0.21	0.39	
Biochemistry	7.31	0.19	0.19	0.33	
Average weekly cost by health state (£)		49.84	19.19	21.47	Calculation
PFS, progression-free survival; Tx, treatment					

3.4.10.3.1 Adverse event costs

A one-off adverse event-related cost was calculated based on the proportion of patients experiencing Grade ≥3 AEs that occurred in at least 5% of patients for either talquetamab or teclistamab and applied in the first cycle of the economic model. The total AE-related costs were [redacted] and [redacted] for the talquetamab and teclistamab arms. The AE costs used in the model are summarised in Table .

Table 40: Adverse event unit costs in the economic analysis, Table 67, CS (pg. 165)

Adverse event	Unit cost (£)	Source
Anaemia	1,772.73	National Schedule of NHS Costs 2023-24, SA09: Weighted Average of Non-Elective Admissions
Hypertension	774.04	National Schedule of NHS Costs 2023-24, EB04Z: Weighted Average of Non-Elective Admissions
Hypokalaemia	2,061.89	National Schedule of NHS Costs 2023-24, KC05J - Fluid or Electrolyte Disorders: Weighted Average of Non-Elective Admissions
Hypophosphatemia	2,061.89	Assumed equal to hypokalaemia (per TA658) [44]

Infection	2,528.21	National Schedule of NHS Costs 2023-24, WJ03A-F: Weighted Average of Non-Elective Admissions
Leukopenia	2,058.10	National Schedule of NHS Costs 2023-24, SA08: Weighted Average of Non-Elective Admissions
Lymphopenia	2,058.10	National Schedule of NHS Costs 2023-24, SA08: Weighted Average of Non-Elective Admissions
Neurotoxicity	7,310.00	Assumed equivalent to the cost of three ICU Days. ICU Costs were sourced from NHS Reference Costs 2023-24 (Weighted Average of XC01Z-07Z, Non-Specific Critical Care)
Neutropenia	2,522.56	National Schedule of NHS Costs 2023-24, SA35: Weighted Average of Non-Elective Admissions
Pneumonia	1,367.85	National Schedule of NHS Costs 2023-24, CB02: Weighted Average of Non-Elective Admissions
Rash	511.89	National Schedule of NHS Costs 2023-24, JD07A-K Weighted Average of Non-Elective Short Stays
Thrombocytopenia	2,515.70	National Schedule of NHS Costs 2023-24, SA12: Weighted Average of Non-Elective Admissions
Weight loss	577.91	National Schedule of NHS Costs 2023-24, FD04A-E Weighted Average of Non-Elective Short Stays
ICU, intensive care unit; NHS, National Health Service		

The company modelled the impact of infections through patient hospitalisations as well as through IVIg usage. The company stated that due to the mechanism of action of talquetamab, patients experience less severe infections compared to patients on teclistamab and thus, require less IVIg to manage their symptoms. Following trial commencement, [redacted] of patients receiving talquetamab underwent IVIg compared to a significantly higher proportion of patients ([redacted]) receiving IVIg in MajesTEC-1. The IVIg dosing schedule applied in the model (9 doses) aligns with the committee's dosing preferences in TA1015. The IVIg acquisition costs are presented in Table 41.

Table 41: IVIg drug acquisition costs, Table 69, CS (pg. 167)

IVIg	Units	Strength	Price per pack or unit cost (£)	Dosage per administration	Drug or monitoring cost	Source
Octagam	1	10.0 g	690.00	[redacted]	[redacted]	BNF 2025

3.4.10.4 Subsequent treatments

Following the two-stage adjustment approach outline in NICE TSD 16, the company adjusted the survival times of patients who received additional therapies not routinely available in UK clinical practice.

The proportion of patients receiving subsequent therapies in both the talquetamab and teclistamab arm are presented in Table 26 of the CS. In the economic model, [redacted] of patients in the talquetamab arm and [redacted] of patients in the teclistamab arm were modelled to receive subsequent therapies following disease progression for an average duration of 4 months, in line with Yong et al. (2016) and NICE committee preferences in TA1015.[6, 45]

For patients receiving teclistamab as a subsequent therapy, the average duration of treatment was [redacted] months as it is deemed more effective than the alternative therapies and thus, patients would be expected to remain on it for a longer period.

To explore the uncertainty surrounding subsequent treatments on the economic analysis, the company explored three additional scenarios:

1. **All-in scenario:** patients receive both teclistamab and talquetamab as subsequent therapies following treatment discontinuation.
2. **All-out:** patients do not receive talquetamab or teclistamab as a subsequent therapy following treatment discontinuation.
3. **70%20%/10% treatment distribution split** for PomDex/PanBorDex/SelDex.

Overall, the EAG agrees with the company's approach for applying costs in the model.

For patients in the PFS health state, the frequency of monitoring resources depended on whether patients were on or off treatment. However, clinical advice to the EAG suggests that haematologist follow-up visits depend on patients' response to treatment, with patients with higher response requiring fewer visits. The EAG were unable to provide their own monitoring resource use frequency and accepts the assumptions made by the company.

The EAG note that the company modelled the impact of infections through patient hospitalisations and IVIg treatment. The EAG were concerned that modelling infections twice could potentially give rise to double counting as there may be an overlap between the two costs. Furthermore, the EAG considers that the company's approach to modelling IVIg usage as a one-off cost underestimates IVIg costs in favour of talquetamab. Clinical advice to the EAG suggests that patients on talquetamab and teclistamab could routinely undergo IVIg to manage infections during treatment and possibly for some period after stopping treatment. However, the real-world studies from Germany and France showed that a higher proportion participants received teclistamab required IVIg.[38];[39];[37]

The EAG noted that IVIg usage was captured for patients receiving first-line talquetamab and teclistamab but not for patients receiving teclistamab as a subsequent therapy following discontinuation from talquetamab. Given that teclistamab was associated with higher IVIg usage, the EAG were concerned that the company's approach of excluding subsequent IVIg could underestimate the costs for the talquetamab arm and requested data on IVIg usage in patients receiving teclistamab as a subsequent therapy. In their clarification response, the company stated that this data was not captured and explored a scenario whereby the proportion of patients receiving subsequent teclistamab following talquetamab requiring IVIg is assumed to be equal to the proportion of patients on first-line teclistamab who required IVIg. Clinical advice to the company stated that the duration of subsequent treatment would be shorter than initial treatment due to disease relapse and patients approaching end of treatment pathway. Therefore, patients are expected to receive fewer IVIg doses compared to the initial 9 doses assumed. The EAG notes that assuming 6 doses increases the ICER by 2%.

The EAG considers that the all-in scenario will allow for an equitable comparison between the two interventions. The company justifies the inclusion of teclistamab as a subsequent therapy without providing a reference to UK SoC or an established guideline for 5th line treatment in TCR RRMM patients who have failed 4th line therapy. Clinical advice to the EAG suggests that teclistamab has been approved as a treatment option for patients in the 4th line RRMM setting, and there is little evidence of its routine use in UK clinical practice beyond this setting. It is not clear whether a 5th line SoC for RRMM exists, as evidenced by MonumenTAL-1 participants receiving many different subsequent treatments. Clinical advice to the EAG indicates that treatment decisions are influenced by a patient's prior lines of therapy and the treating clinician's judgement. Furthermore, according to RWE study from Germany and France, most patients received BCMA-directed therapies followed by GPRC5D as a salvage therapy.[38];[39];[37] Clinical expert advice to the EAG suggests that the positioning of talquetamab in UK clinical practice is likely to follow this order and patients would be offered a GPR5CD therapy after failing a prior line of BCMA-targeted therapy.

Clinical advice to the EAG is of the opinion that if talquetamab is positioned in 4th line and patients are not responding, a BCMA-directed therapy such as teclistamab may be used in the 5th line for patients with no prior BCMA exposure. However, there is no prominent real-world data on this reverse order sequencing and the cohort of patients who have talquetamab exposure followed by teclistamab is too small to be able to draw meaningful conclusions about the effectiveness of this strategy.

As mentioned previously, the EAG was concerned that not capturing IVIg usage in subsequent teclistamab therapy may significantly underestimate the costs in the model. Clinical advice to the EAG suggests that patients on talquetamab and teclistamab are expected to routinely receive IVIg during treatment, with an

estimated frequency of one dose a month. The EAG prefers to model subsequent IVIg usage in patients receiving talquetamab and teclistamab as subsequent treatments, assuming 6 and 9 doses of IVIg respectively in line with the duration of subsequent treatment.

3.4.11 Severity modifier

The company calculated the absolute and proportional QALY shortfalls for people with TCE RRMM. Based on the calculations the absolute and proportional shortfalls were [redacted]years and [redacted], respectively, which are less than the threshold of 12 years and 0.85; indicating that talquetamab when compared to teclistamab does not meet the severity modifier threshold.

3.4.12 Overview of model assumptions and EAG critique

The EAG critique of model assumptions is provided in Table 42.

Table 42: EAG critique of model assumptions

Parameter	*Assumption*	*Justification*	*EAG critique*
Survival models			
OS, PFS and TTD curves	*Teclistamab OS, PFS and TTD is modelled by independent extrapolation of the OS data from MajesTEC-1, using the calibrated LogNormal curve, as accepted by the Committee in TA1015.*[6] *Talquetamab OS, PFS and TTD is modelled by applying the respective HRs estimated from the ITC for talquetamab versus teclistamab (post-two stage adjustment for OS) to the teclistamab extrapolation described above.*	*The modelling of teclistamab OS, PFS and TTD was aligned with and builds upon the Committee accepted approach in TA1015.*[6] *The trial versus trial ITC results represent the highest grade of evidence estimates of the relative effects between talquetamab and teclistamab, and therefore it was considered most appropriate to apply the HR from the ITCs (two-stage adjusted for OS) to the extrapolations for teclistamab OS. The Schoenfeld residual plot was horizontal with a p-value >0.05 for OS, PFS and TTD, providing no evidence that the PH assumption should be rejected, in turn justifying the HR approach.*	The company's choice and use of lognormal models. First, the company adopted PH approach and applied this to an AFT lognormal model fitted to the teclistamab OS data, then generated talquetamab OS. Second, the unadjusted lognormal for modelling talquetamab OS produces implausible estimates of [redacted] of participants remain alive at 40 years. The company's lognormal model was calibrated to fit clinical prediction; an unnecessary restriction on full exploration of the available evidence. To model teclistamab PFS beyond the observation period the company base-case selected a lognormal model that was forced by calibration to fit clinician predictions of the percentage of progressed patients at 10 and 15 years (5% and 1%, respectively. Without calibration, the lognormal model seems implausibly optimistic (see Figure 16). The EAG considers the Weibull model preferable: first, it fits closely with the clinical predictions whereas the lognormal model is forced to comply with opinion-based calibration.

Parameter	*Assumption*	*Justification*	*EAG critique*
			Second, the Weibull model supports the proportion hazards approach adopted by the company whereas the lognormal AFT model is less suited. The lognormal models predicated on the TA1015 approach generate unrealistic OS and PFS for teclistamab
Two-stage OS subsequent treatment adjustment	*Owing to the international nature of MajesTEC-1 and MonumenTAL-1, patients received subsequent therapies which are not available in routine UK clinical practice. The effects of these subsequent treatments on OS were removed using the two-stage OS adjustment approach outlined in NICE TSD16 to inform the economic base case.*[26]	*This two-stage OS adjustment is in line with the accepted approach in TA1015, wherein the teclistamab OS data was similarly adjusted for patients initiating a subsequent treatment not available in routine UK clinical practice.*[6] *Following the two-stage OS adjustment, as detailed in Section* ***Error! Reference source not found.****, a range of scenario analyses exploring alternative subsequent treatment adjustments, demonstrated consistent OS HRs and ICERs in favour of talquetamab. The scenario analyses explored included (a) an 'All-Out' scenario, with the removal of non-UK subsequent therapies, including removal of subsequent teclistamab and talquetamab in*	Please see the EAG's comment to '*Proportion of patients receiving subsequent treatment and distribution of subsequent treatments.'*

Parameter	Assumption	Justification	EAG critique
		MonumenTAL-1 and MajesTEC-1, respectively as well as (b) an 'All-In' scenario, which allowed for subsequent talquetamab in MajesTEC-1 to be considered. Results of these scenario analyses are presented above in Section ***Error! Reference source not found.*** *(OS ITC analyses) and Section* ***Error! Reference source not found.*** *(cost-effectiveness results).*	
Costs			
Hospitalisation for talquetamab and teclistamab step-up dosing	*A hospitalisation period of 8 days and 6 days were assumed for the step-up dosing regimen of talquetamab and teclistamab respectively.*[1]	*The hospitalisation periods for teclistamab and talquetamab are aligned with the respective SmPCs and the approach taken in TA1015 for teclistamab.*[1, 6, 46]	The EAG considers these assumptions reasonable.
Teclistamab dose switching	*A reduced dose frequency of teclistamab (i.e. biweekly dosing) was modelled starting from 52 weeks, using the Gompertz dose switching curve, as accepted in TA1015. The remaining patients were assumed to remain on a weekly dosing regimen*	*As per the Committee's preferred approach in TA1015, a reduced dose frequency of teclistamab (i.e. biweekly dosing) was modelled from 52 weeks using the MajesTEC-1 data (IPTW ATT-weighted) to model the reduced dose frequency at different time points from 52 weeks onwards.*[47]	

Parameter	Assumption	Justification	EAG critique
Dose skipping	*The model included a proportion of talquetamab doses being skipped based on MonumenTAL-1, wherein [redacted]% of talquetamab doses were skipped.*[16] *A proportion of teclistamab doses being skipped was also modelled based on MajesTEC-1, wherein [redacted]% of teclistamab doses were skipped in line with the Committee preferred assumptions for TA1015.*[13]	*In line with the Committee accepted approach in TA1015, skipped doses of both teclistamab and talquetamab were accounted for in the base case.*[6]	
Proportion of patients receiving subsequent treatment and distribution of subsequent treatments	*The proportion of patients receiving subsequent treatments following progression on teclistamab and talquetamab is based on MajesTEC-1 and MonumenTAL-1, respectively.*[13, 16] *The distribution of subsequent treatments was based on the trials but adjusted following the removal of non-routine UK therapies.*	*MonumenTAL-1 and MajesTEC-1 represent the best evidence sources to inform the proportion of patients receiving subsequent treatment following progression on talquetamab and teclistamab, respectively. However, it is acknowledged that patients in MonumenTAL-1 and MajesTEC-1 received therapies which are not available in routine UK clinical practice and therefore, the costs for subsequent treatment have been calculated based on the*	While the EAG agree with excluding subsequent treatments following progression on teclistamab and talquetamab based on the MajesTEC-1 and MonumenTAL-1 trials, respectively; we consider that the company's approach by excluding subsequent talquetamab but including subsequent teclistamab treatment creates an inequitable approach in favour of talquetamab. For a fair comparison of the competing interventions each arm should be considered equitably. In the absence of an RCT and just the two single-arm studies in the submission, it is difficult to achieve this, as exemplified by the

Parameter	Assumption	Justification	EAG critique
		subsequent treatment distribution following the removal of non-routine UK therapies in line with the approach taken in TA1015.[6]	complicated set of adjustments introduced in the submission. If an RCT had been, or were to be undertaken, then the trial design would likely allow reciprocal switching to the alternative treatment at some stage. In fact, a crossover RCT would be predicated on this.
Subsequent treatment duration	*Following disease progression on talquetamab or teclistamab, patients were assumed to receive subsequent treatments (other than teclistamab) for a mean duration of 4 months, in line with Yong et al. 2016 and TA1015.*[6, 45]*, The mean duration of treatment on teclistamab was assumed to be* [redacted] *(SE:* [redacted]*) months, based on MonumenTAL-1.*[16]	*The subsequent treatment duration assumption of 4 months for the non-teclistamab subsequent therapies is in line with the Committee accepted approach in TA1015.*[6] *It is acknowledged that given that teclistamab has been shown to be more effective than the other subsequent treatment options, patients receiving teclistamab are likely to receive treatment for a longer duration and therefore, it was deemed more appropriate to model the duration of treatment on teclistamab based on MonumenTAL-1 trial data.*[16] *Likewise, in the 'All-In' scenario analysis, the duration of subsequent treatment with talquetamab after teclistamab was modelled based on MonumenTAL-1 trial data (*[redacted] *[SE:* [redacted]*]) months).*[16]	There is absence of evidence regarding the duration of subsequent treatments, the depth of their effect, and how these effects extend over the lifetime horizon of 40 years.

Parameter	Assumption	Justification	EAG critique
IVIg	*Ig costs were modelled in line with the usage of IV Ig observed in MajesTEC-1 ([redacted]%) and MonumenTAL-1 (Cohort C; [redacted]%)].[13] The average number of doses was assumed to be 9 doses, in line with the Committee accepted approach in TA1015.[6]*	*In the absence of available data on Ig usage in TCE RRMM patients in UK clinical practice, the MajesTEC-1 and MonumenTAL-1 trials, in addition to the duration of IVIg use agreed in TA1015 were considered as the best source of data to inform Ig usage in the economic model.[13]*	In the absence of submitted relevant evidence the EAG assumes that IVIg use is undertaken to mitigate effects of infection. Since it can only be received by live patients the main drivers of IVIg usage will be the amount of infection and the survival of patients. At data cut-off (after about 40 months) 71% of Cohort C had had an infection (CS Table 49) and at [redacted] months (CS Table 29) [redacted] were still alive and able to receive IVIg, while at MajesTEC-1 at data cut off [redacted] had had an infection and only [redacted] were still alive (CS Figure 27). From these data, the EAG concludes that in the relatively short term (3.5 years) IVIg usage would be greater for talquetamab recipients (Cohort C) than for teclistamab recipients. Beyond 40 months, infections are unlikely to cease, and IVIg use would not be precluded; there is likely to be continued use of IVIg (at 40 months). Since the company model shows that by 15 years (CS Figure 27) only about [redacted] of teclistamab arm remain alive compared with [redacted] of talquetamab (Cohort C) arm, the EAG concludes that use of IVIg would be greater for talquetamab arm than for teclistamab arm patients irrespective of any

Parameter	Assumption	Justification	EAG critique
			subsequent treatments they may or may not receive. The EAG concludes that company's submitted evidence indicates there will be substantially more use of IVIg for talquetamab arm patients than for teclistamab arm patients, and that this should reflected in some way the economic analysis. Furthermore, real world studies from France[38] and Germany[37, 39] suggest that prophylaxis with IVIg may be routine in practice to mitigate against infections in immune-compromised MM patients and to avoid interruptions in the use of effective MM therapies. However, we noted that [redacted] (re-weighted to adjust for treatments available in the UK) of participants in the talquetamab trial received subsequent teclistamab treatment, but the company did not include any resource use and costs associated with IVIg treatment for these participants. Thus, we consider that the ICER to have been underestimated (not capturing all costs associated with treatment. At clarification, the company stated that IVIg use was not explicitly collected for participants who received IVIg as part of subsequent treatment in

Parameter	*Assumption*	*Justification*	*EAG critique*
			the MonumenTAL-1 trial. Hence, no data are available on the proportion of participants who received subsequent teclistamab treatment who required IVIg treatment. In the absence of these data, they undertook several scenario analyses. In the absence of data, we assumed that the proportion of people receiving IVIg with subsequent teclistamab to be consistent with those receiving IVIg with initial teclistamab treatment ([redacted]). People receiving subsequent teclistamab treatment were assumed to receive six IVIg doses. In the EAG base-case, we included subsequent talquetamab treatment and assumed that the proportion of people receiving IVIg with subsequent talquetamab to be consistent with those receiving IVIg with initial talquetamab. People receiving subsequent talquetamab treatment were assumed to receive nine IVIg doses.

Parameter	Assumption	Justification	EAG critique
Utility values			
Treatment-independent HSUVs	*In the base case analysis, treatment-independent HSUVs, derived from MonumenTAL-1 were used to inform the utility values for teclistamab and talquetamab.*	*Given that talquetamab and teclistamab are both BsAbs and dexamethasone-free regimens, it was deemed appropriate to assume equal utilities. Utility values for the PF and PP health states were derived using EQ-5D-5L data in MonumenTAL-1.*[16] *The use of treatment-independent HSUVs informed by MajesTEC-1 was explored in a scenario analysis (see Section* ***Error! Reference source not found.****).*[22]	The EAG considers this approach reasonable.
AE disutilities	*In the base case analysis, to account for the impact of treatment-specific of AEs, a one-off decrement in utilities was applied based on the proportion and duration of AEs experienced by patients in MonumenTAL-1 and MajesTEC-1.*[13, 16] *Utility decrements were informed by published literature, in line with the Committee accepted approach in TA1015.*[6]	*Whilst both talquetamab and teclistamab are BsAbs and dexamethasone-free monotherapies, differences in the safety profile of both therapies remain. To account for the differences in AEs experienced by patients receiving each treatment, it was deemed appropriate to apply a one-off decrement in utilities.*	Utility values were estimated from EQ-5D-5L information collected in the MonumenTAL-1 trial; thus, the inclusion of AE disutilities may result in double counting.

Parameter	*Assumption*	*Justification*	*EAG critique*
AEs, adverse events; BsAbs, bispecific antibodies; CRS, cytokine release syndrome; EQ-5D-5L, EuroQol five dimensions five levels; HR, hazard ratio; HSUVs, health state utility values; IVIg, intravenous immunoglobulin; NICE, National Institute for Health and Care Excellence; OS, overall survival; PF, progression-free; PFS, progression-free survival; PP, post-progression SmPC, Summary of Product Characteristics; TTD, time to treatment discontinuation; TSD, Technical Support Document			

4 COST EFFECTIVENESS RESULTS

The company reported deterministic, sensitivity (including probabilistic) and scenario analyses results for the comparison between talquetamab versus teclistamab. Main outcomes were reported in terms of costs, life-years and QALYs, with the overall results reported in the form of an incremental cost-effectiveness ratio (ICER) expressed as cost per QALY. Results were also reported in terms of net health benefit assuming a threshold of £30,000.

In the company submission, results have been reported based on list prices and patient access scheme prices for talquetamab and teclistamab.

4.1 Company's cost effectiveness results

4.1.1 Company's deterministic base-case results

The results in Table shows that under list prices, treatment with talquetamab is [redacted] more expensive than teclistamab and expected to yield [redacted] more QALY, which equates to an ICER of £64,459 per QALY. As expected, including the PAS agreements resulted in a reduction to the total costs with no change to the LYs or QALYs. Using PAS prices, treatment with talquetamab is [redacted] more expensive than teclistamab and expected to yield [redacted] more QALYs, which results in an ICER of £29,277 per QALY (see Table 44).

It should be noted that using the PAS agreements also resulted in the INHB becoming positive, which indicates that the health gain is greater than that from investing the same resources in an alternative cost-effective technology under a £30,000 threshold.

Table 43: Company deterministic base-case results, using list prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	6.27	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£64,459	-2.25
ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained								

Table 44: Company deterministic base-case results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	6.27	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	3.05	[redacted]	[redacted]	3.22	[redacted]	£29,277	0.05
ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained								

4.2 Company's sensitivity analyses

4.2.1 Company's probabilistic sensitivity analysis results

PSA was undertaken for the outcome cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters. The PSA results were reported in tabular form under list prices and PAS prices, separately, and iterations presented on scatterplots, with their corresponding cost-effectiveness acceptability curves (CEACs). The PAS results in Table 45 and Table 46, are in line with the deterministic results.

PSA results presented on an incremental cost-effectiveness plane (see Figure 37) showed that the majority of the iterations are in the north-east quadrant, which indicates that treatment with talquetamab is likely to be more costly and more effective compared to treatment with teclistamab. Corresponding results are reported in the form of a CEAC (see Figure 38), which show that talquetamab has a [redacted] probability of being cost-effective compared to teclistamab at a willingness-to-pay threshold of £30,000 per QALY and a [redacted] probability of being cost-effective compared to teclistamab at a willingness-to-pay threshold of £20,000 per QALY.

The parameters included in the PSA along with their respective distributions appear to be appropriate. However, the EAG noted that the standard errors around the health state utility values appeared small however given the paucity of information about how these were derived from the EQ-5D-5L obtained from participants, the EAG were unable to decipher if these values reflected the true uncertainty. Additionally, the company stated that OS, PFS and TTD are 'inherently interlinked parameters, with changes in one parameter likely also leading to changes in another, the uncertainty around the HRs cannot be fully measured by considering the one-way sensitivity analysis', but it was unclear if/how this interlink was captured in the company's PSA.

Table 45: Company probabilistic sensitivity analysis results, using list prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	6.34	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£64,760	-2.32

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained

Table 46: Company probabilistic sensitivity analysis results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	6.34	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	3.04	[redacted]	[redacted]	3.29	[redacted]	£29,246	0.05

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained

Figure 37: Incremental cost-effectiveness scatterplot for the comparison between talquetamab versus teclistamab

Figure 38: Cost-effectiveness acceptability curve

4.2.2 Deterministic sensitivity analysis

The company undertook one-way sensitivity analysis by varying key model input parameters, and the results were reported in the form of tornado diagrams for the outcome the ICER and incremental net health benefit assuming a willingness-to-pay threshold of £30,000.

The impact on the company's base-case ICER is presented in Figure 39. These results showed that the HRs for time-to-treatment discontinuation (TTD) and OS had the greatest impact on the company's base-case ICER, under PAS agreements. Considering the lower bound value of [redacted] for HR for TTD [redacted] the ICER to [redacted] per QALY, while the upper bound value [redacted] to ICER to [redacted] per QALY.

The EAG considers the company's list of inputs included in the OWSA to be comprehensive and that the most influential inputs were presented on the tornado diagram.

Figure 39: Company tornado diagram for the comparison between talquetamab versus teclistamab

4.2.2.1.1 **Scenario analysis results**

The company undertook several scenario analyses to further understand the robustness of the results to making changes to key assumptions and alternative inputs. In Table 47, we present the company's scenario analysis results.

Results are reported based on the outcome cost per QALY and INHB assuming a WTP threshold of £30,000 per QALY.

Table 47: Company deterministic scenario analysis results for talquetamab versus teclistamab, using PAS prices

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
Base-case		[redacted]	[redacted]	£29,277	[redacted]
1.	Time horizon: 25 years	[redacted]	[redacted]	£29,561	[redacted]
2.	Time horizon: 30 years	[redacted]	[redacted]	£29,294	[redacted]
3.	Talquetamab efficacy data source: Weighted split 90%/10% Cohort C and A	[redacted]	[redacted]	£29,580	[redacted]
4.	Utility values: Derived from MajesTEC-1	[redacted]	[redacted]	£30,926	[redacted]
5.	AE disutilities: No decrements applied	[redacted]	[redacted]	£29,421	[redacted]
6.	Subsequent treatment: Reweighting non-teclistamab subsequent treatment (i.e. 70%/20%/10% split for PomDex/PanBorDex/SelDex)	[redacted]	[redacted]	£31,175	[redacted]
7.	Subsequent treatment: Removal of all non-routine UK treatment, as well as removing teclistamab from MonumenTAL-1 – All Out	[redacted]	[redacted]	£31,280	[redacted]
8.	Subsequent treatment: Removal of all non-routine UK treatment, but allowing subsequent	[redacted]	[redacted]	£29,109	[redacted]

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
	talquetamab following teclistamab, vice versa – All In				
9.	Talquetamab PFS/OS/TTD: Individually fitted Lognormal	[redacted]	[redacted]	£23,675	[redacted]
10.	Talquetamab PFS/OS/TTD: Individually fitted Weibull	[redacted]	[redacted]	£22,631	[redacted]
11.	Talquetamab PFS/OS/TTD: Individually fitted Gamma	[redacted]	[redacted]	£25,361	[redacted]
INHB, incremental net health benefit; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation					

4.3 Model validation and face validity check

Several validity checks were undertaken by the company, including face validity, internal and external validity. The company claims that the model structure, data and statistical analysis designs were reviewed by health economic and clinical experts. Internal validity in the form of technical validation was undertaken to ensure the model generated outcome results consistent with the clinical and economic inputs. This included checks of model interface, mathematical calculations and Visual Basic for Applications (VBA). Additionally, the running of sensitivity and scenario analyses were reviewed along with extreme value testing to evaluate the model's responses to changes to inputs.

The company also undertook external validation by seeking clinical expert opinion on their key model inputs, subsequent treatment choices and monitoring frequencies as well as modelling assumptions. However, it was not clear to the EAG if the company received clinical expert feedback on the results produced by the economic analysis. In the EAG's critique, our clinical experts noted that there were little differences in the PFS curves for talquetamab and teclistamab given that there were more infection-related deaths in participants treated with teclistamab compared to talquetamab and this was not seen in the PFS curves.

The EAG also sought expert opinion on the overall model outputs on expected life years over the model time horizon, which they suggested appeared high given the age and severity of the population.

4.4 Conclusion of company cost-effectiveness sections

The EAG assessed the company's economic evidence submitted, which included the systematic review of published economic evidence, the company's evidence, and the company's model. No attempt was made to appraise the company's budget impact analysis.

The company's submission is based on an economic evaluation of talquetamab compared to teclistamab for treating people with RRMM. While the illustrative model structure depicts the logical clinical pathway for treating people with RRMM, we identified several clinical concerns that transcend the cost-effectiveness issues, together with concerns in the economic evidence leading to potential biases in favour of talquetamab, which we have documented in Table 48Table 48:

Table 48: Issues identified by the EAG

ID2725	Summary of issues	Report section	EAG recommendation
Clinical effectiveness			
Modelling of OS	The company's choice and use of lognormal models. First, the company adopted PH approach and applied this to an AFT lognormal model fitted to the teclistamab OS data, then generated talquetamab OS. Second, the unadjusted lognormal for modelling talquetamab OS produces implausible estimates of [redacted] of participants remain alive at 40 years. The lognormal models predicated on the TA1015 approach generate unrealistic OS and PFS for teclistamab. However, the company state that resultant talquetamab extrapolations after applying the ITC HRs to the calibrated ATT-weighted teclistamab extrapolations were then capped for GPM.	Sections 3.4.5 and 3.4.6	The EAG considers the uncalibrated Weibull model a more suitable choice for use in modelling teclistamab and using the company's hazard ratio approach to generate OS for people treated with talquetamab.
Modelling of PFS	The teclistamab PFS beyond the trial observation period was modelled using a lognormal parametric curve, which was	Section 3.4.7	The EAG considers the uncalibrated Weibull model a more suitable choice for use in

ID2725	Summary of issues	Report section	EAG recommendation
	forced by calibration to fit clinical expert opinion on predictions of the percentage of progressed patients at 10 and 15 years (5% and 1%, respectively. Without calibration, the lognormal model seems implausibly optimistic (see Figure 16). The lognormal models predicated on the TA1015 approach generate unrealistic OS and PFS for teclistamab		modelling PFS for teclistamab and talquetamab. First, it fits closely with the clinical predictions whereas the lognormal model is forced to comply with opinion-based calibration. Second, the Weibull model supports the proportion hazards approach adopted by the company whereas the lognormal AFT model is less suited.
Modelling of TTD	The company chose the lognormal modelling of teclistamab and talquetamab TTD. The lognormal model, if not adjusted, predicts people on treatment beyond 20 years and a few beyond 30 years, which the EAG consider implausible. To make these predictions plausible, the company adjusted the lognormal model by calibrating to the clinical experts predictions of the number of people expected to be on treatment at 10 years and 15 years.	Section 3.4.7.4	Uncalibrated extrapolated Weibull and gamma models provide reasonable fit to clinical prediction; in so doing they have advantage over calibrated lognormal models that require forcing by calibration. The Weibull and gamma models are more suited than lognormal for application of a proportional hazards approach.
Cost-effectiveness			
Half-cycle correction	The company model cycle length was weekly, and a half-cycle correction was applied to health outcomes and costs to account for mid-cycle progressions. The EAG considers that the application of a half-cycle correction is not necessary when the cycle length is weekly.	Section 3.4.4	The cycle length is one week and the EAG considers it not necessary to apply a half-cycle correction to account for mid-cycle transitions.
Discounting	The company applied discounting in the first year of the economic analysis.	Section 3.4.4	Apply discounting from Year 1 onwards. No discounting should be

ID2725	Summary of issues	Report section	EAG recommendation
			applied to the current year as the relevant costs and benefits are already in the present value.
Additional IVIg treatment	[redacted] (re-weighted to adjust for treatments available in the UK) of participants in the talquetamab trial received subsequent teclistamab treatment. However, the company did not include any IVIg treatment for these participants. At clarification, the company stated that IVIg use was not explicitly collected for participants who received IVIg as part of subsequent treatment in the MonumenTAL-1 trial. Hence, no data are available on the proportion of participants who received teclistamab as a subsequent treatment following talquetamab who required IVIg treatment. In the absence of these data, they undertook several scenario analyses.	Table 42 and Section 3.4.10.4	In the absence of submitted relevant evidence the EAG assumes that IVIg use is undertaken to mitigate effects of infection. Since it can only be received by live patients the main drivers of IVIg usage will be the amount of infection and the survival of patients. At data cut-off (after about [redacted] months) 71% of Cohort C had had an infection (Table 49) and at [redacted] months (Table 29) [redacted] were still alive and able to receive IVIg, while at MajesTEC-1 at data cut off [redacted] had had an infection and only [redacted] were still alive (Figure 27). From these data, the EAG concludes that in the relatively short term (3.5 years) IVIg usage would be greater for talquetamab recipients (Cohort C) than for teclistamab recipients. Beyond 40 months, infections are unlikely to cease, and IVIg use would not be precluded; there is likely to be continued use of IVIg (at

ID2725	Summary of issues	Report section	EAG recommendation
			40 months). Since the company model shows that by 15 years (Figure 27) only about 3% of teclistamab arm remain alive compared with 19% of talquetamab (Cohort C) arm, the EAG concludes that use of IVIg would be greater for talquetamab arm than for teclistamab arm patients irrespective of any subsequent treatments they may or may not receive. The EAG concludes that company's submitted evidence indicates there will be substantially more use of IVIg for talquetamab arm patients than for teclistamab arm patients, and that this should reflected in some way the economic analysis. Furthermore, real world studies from France[38] and Germany[37, 39] suggest that prophylaxis with IVIg may be routine in practice to mitigate against infections in immune-compromised MM patients and to avoid interruptions in the use of effective MM therapies. In the absence of data, we assumed that the proportion of people receiving IVIg with subsequent teclistamab

ID2725	Summary of issues	Report section	EAG recommendation
			to be consistent with those receiving IVIg with initial teclistamab treatment ([redacted]). People receiving subsequent teclistamab treatment were assumed to receive nine IVIg doses, i.e., the same number of IVIg doses as initial teclistamab treatment and in line with the duration that people received subsequent teclistamab. Additionally, people receiving subsequent talquetamab treatment were assumed to receive six IVIg doses. This is in line with the duration that people received subsequent talquetamab.
Exclusion of subsequent talquetamab treatment	Excluding subsequent talquetamab in the teclistamab arm while allowing teclistamab in the talquetamab arm is inequitable procedure between arms.	Section 3.4.10.4	Include subsequent talquetamab treatment for a fair comparison of the competing interventions. First, there is no established SoC for this subgroup. Second, the company are expressing an opinion about what SoC might be. Third, without providing a reference to UK SoC or to a UK guideline for 5th line treatment in this small defined subgroup the EAG consider the company's rationale invalid. Fourth, the lack of an accepted SoC is well exemplified by the

ID2725	Summary of issues	Report section	EAG recommendation
			large number (80+) different subsequent therapies received by MonumenTAL-1 patients (as listed in the submitted Appendix document).
AEs disutility	The company's base-case analysis includes AEs disutilities.	Section 3.4.9.1	Utility values were estimated from EQ-5D information collected in the MonumenTAL-1 trial; thus, the inclusion of AE disutilities may result in double counting.
AE, adverse event; EAG, evidence assessment group; EQ-5D, EuroQoL five dimension; IVIg, intravenous immunoglobulin; OS, overall survival; PFS, progression-free survival; SoC, standard of care; TA, technology appraisal; TTD, time-to-treatment discontinuation			

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG undertook further exploratory scenario analyses around the company's base-case, with these results reported in Table 49. These results show that the company's ICER is sensitive to the talquetamab versus teclistamab OS HR.

Table 49: EAG scenario analyses based on the company's base-case results

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
Base-case		[redacted]	[redacted]	£29,277	0.05
1.	Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment	[redacted]	[redacted]	£33,500	[redacted]
2.	Talquetamab vs teclistamab OS HR is 0.55	[redacted]	[redacted]	£35,075	[redacted]
3.	Talquetamab vs teclistamab OS HR is 0.60	[redacted]	[redacted]	£41,134	[redacted]
4.	Talquetamab vs teclistamab OS HR is 0.65	[redacted]	[redacted]	£48,893	[redacted]
5.	Talquetamab vs teclistamab OS HR is 0.70	[redacted]	[redacted]	£59,167	[redacted]
6.	Talquetamab vs teclistamab OS HR is 0.75	[redacted]	[redacted]	£73,425	[redacted]
7.	Talquetamab vs teclistamab OS HR is 0.80	[redacted]	[redacted]	£94,516	[redacted]
8.	Talquetamab vs teclistamab OS HR is 0.85	[redacted]	[redacted]	£128,856	[redacted]
9.	Talquetamab vs teclistamab OS HR is 0.90	[redacted]	[redacted]	£194,755	[redacted]

INHB, incremental net health benefit; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

Additionally, in Table 50 we report the company's preferred assumptions/information used in their base-case for some of the model inputs, along with the EAG's preferences.

Table 50: EAG's changes made to the company's base-case model

Variable	Company's Value	EAG's value/approach	Reference to related issue in
Clinical effectiveness			
Overall survival (OS)			
OS	Calibrated lognormal modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS	Uncalibrated Weibull modelling of OS	Sections 3.4.5 and 3.4.6
Progression-free survival (PFS)			
PFS	Calibrated lognormal modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS	Uncalibrated Weibull modelling of PFS	Section 3.4.7
Time-to-treatment discontinuation (TTD)			
TTD	Calibrated lognormal modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD	Uncalibrated Weibull modelling of TTD	Section 3.4.7.4
Cost-effectiveness			
Half-cycle correction	Include half-cycle correction	Exclude half-cycle correction	Section 3.4.4
Discounting	Discounting was applied in the first year	Discounting from Year 1 onwards	Section 3.4.4
Additional IVIg treatment	No IVIg treatment for people who received subsequent treatment	We assumed that the people who received subsequent talquetamab and teclistamab treatment would require IVIg treatment. In the absence of data, we assumed that [redacted] of people who received subsequent talquetamab treatment would require IVIg treatment and [redacted] of people who received subsequent teclistamab treatment would require IVIg treatment.	Table 42 and Section 3.4.10.4

Variable	Company's Value	EAG's value/approach	Reference to related issue in
Subsequent talquetamab treatment	Excluded subsequent talquetamab in the teclistamab arm. (See Decision Problem – current UK clinical practice)	Include subsequent talquetamab treatment for a fair comparison of the competing interventions.	Section 3.4.10.4
AEs disutility	The company's base-case analysis includes AE disutilities.	The EAGs consider that the inclusion of disutilities associated with adverse events may result in double counting. As such the EAG excluded AE disutilities in their base-case model	Section 3.4.9.1
AE, adverse events; EAG, evidence assessment group; HR, hazard ratio; IVIg, intravenous immunoglobulin; OS, overall survival; PFS, progression, TTD, time-to-treatment discontinuation			

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Table 5151, we report the results of the comparison between talquetamab and teclistamab and the impact of each of the changes made by the EAG.

Table 51: Results of the EAG's exploratory analysis of the company's base-case

EAG's preferred assumption		Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)	Impact to the company's base-case ICER
Company's base-case		[redacted]	[redacted]	£29,277	-
9.	Uncalibrated Weibull modelling of teclistamab OS	[redacted]	[redacted]	£32,437	[redacted]
10.	Uncalibrated Weibull modelling of teclistamab PFS	[redacted]	[redacted]	£28,912	[redacted]
11.	Uncalibrated Weibull modelling of teclistamab TTD	[redacted]	[redacted]	£25,672	[redacted]
12.	No half-cycle correction	[redacted]	[redacted]	£29,492	[redacted]
13.	No discounting in the first year	[redacted]	[redacted]	£29,286	[redacted]
14.	Additional IVIg treatment – talquetamab (6 doses) and teclistamab (9 doses)	[redacted]	[redacted]	£30,157	[redacted]
15.	Inclusion of subsequent talquetamab treatment	[redacted]	[redacted]	£29,109	[redacted]
16.	Exclude AE disutilities	[redacted]	[redacted]	£29,421	[redacted]

AE, adverse events, ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

5.3 EAG's preferred assumptions

The EAG's preferred assumptions include making the following changes simultaneously:

- Uncalibrated Weibull modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS.
- Uncalibrated Weibull modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS.
- Uncalibrated Weibull modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD.
- Exclude half-cycle correction.
- Discounting from Year 1 onwards.
- We assumed that the people who received subsequent talquetamab and teclistamab treatment would require IVIg treatment. In the absence of data, we assumed that [redacted] of people who received subsequent talquetamab treatment would require IVIg treatment and [redacted] of people who received subsequent teclistamab treatment would require IVIg treatment.
- Include subsequent talquetamab treatment for a fair comparison of the competing interventions.
- The EAGs consider that the inclusion of disutilities associated with adverse events may result in double counting. As such the EAG excluded AE disutilities in their base-case model

The EAG's base-case analysis compares talquetamab versus teclistamab, using the PAS agreements in place for talquetamab and teclistamab. In the EAG Appendix, we present a list of analyses applying eMIT prices for subsequent treatments, with the results presented in a separate confidential appendix document.

5.4 EAG deterministic base-case results

In Table 52 we present the EAG's base-case analysis results. These results show that treatment with talquetamab is expected to be [redacted] more expensive compared to teclistamab and expected to yield an additional 2.85 LYs and [redacted] more QALYs, equating to an ICER of £30,106 per QALY.

Table 52: EAG's deterministic base-case results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	5.51	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	2.66	[redacted]	[redacted]	2.85	[redacted]	£30,106	[redacted]

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years **gained**

5.4.1 EAG probabilistic base-case results

In Table 53, we report the PSA results based on the cost per QALY only. These results show that considering all joint uncertainty the PSA results return similar results to the EAG deterministic results. In Figure 40 and Figure 41, we report the corresponding PSA results but in the form of scatter plots plotted on an incremental cost-effectiveness plane, and cost-effectiveness acceptability curve. In Figure 40, these results show that majority of the iterations are in the [redacted] quadrant, signifying that treatment with talquetamab is expected to be more costly and more effective than treatment with teclistamab. Also, the majority of the iterations are above the willingness-to-pay threshold of £30,000 per QALY, with talquetamab having a [redacted] probability of being cost-effective when compared to teclistamab.

Table 53: EAG's probabilistic sensitivity analysis results, using PAS prices

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)	INHB (£30,000)
Talquetamab	[redacted]	5.49	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	2.68	[redacted]	[redacted]	2.81	[redacted]	£31,083	[redacted]

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life-years gained; QALY, quality adjusted life years gained

Figure 40: EAG scatterplot of the comparison between talquetamab versus teclistamab on an incremental cost-effectiveness plane

Figure 41: EAG cost-effectiveness acceptability curve

5.4.2 EAG's one-way sensitivity analysis

In Figure 42, we present the results of the EAG's one-way sensitivity analysis based on the ICER cost per QALY only. Of the parameters varied, using their upper and lower bound, these results show 10 most influential model inputs. As in the company's results, the OS HR and the TTD HR were key drivers of the economic analysis. By changing the upper bound value for OS HR and keeping all other inputs constant resulted in [redacted] to the ICER to approximately [redacted] per QALY. Conversely, using the lower bound value resulted in [redacted] to the ICER of approximately [redacted] per QALY.

5.5 EAG's scenario analysis

In **Error! Reference source not found.**, we present the results of the EAG scenario analyses. These results show that by increasing the talquetamab versus teclistamab OS HR increases the ICER.

Figure 42: EAG tornado diagram for the comparison between talquetamab versus teclistamab

Table 54: EAG's deterministic scenario analysis results for talquetamab versus teclistamab, using PAS prices

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
EAG's base-case		[redacted]	[redacted]	£30,106	[redacted]
1.	Equal to initial doses for people who require IVIg treatment following subsequent talquetamab and teclistamab	[redacted]	[redacted]	£30,091	[redacted]
2.	Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment	[redacted]	[redacted]	£34,129	[redacted]
3.	Exclude unit costs associated with treating infections	[redacted]	[redacted]	£30,432	[redacted]
4.	All out- removal of all non-routine UK treatment and removing teclistamab from MonumenTAL-1	[redacted]	[redacted]	£31,620	[redacted]
5.	Utility values from MajesTEC-1	[redacted]	[redacted]	£31,789	[redacted]
6.	Talquetamab OS/PFS/TTD, individually fitted	[redacted]	[redacted]	£22,256	[redacted]
7.	Talquetamab vs teclistamab OS HR is 0.55	[redacted]	[redacted]	£36,041	[redacted]
8.	Talquetamab vs teclistamab OS HR is 0.60	[redacted]	[redacted]	£42,621	[redacted]

Scenario		Talquetamab versus teclistamab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	INHB (£30,000 per QALY)
9.	Talquetamab vs teclistamab OS HR is 0.65	[redacted]	[redacted]	£51,039	[redacted]
10.	Talquetamab vs teclistamab OS HR is 0.70	[redacted]	[redacted]	£62,174	[redacted]
11.	Talquetamab vs teclistamab OS HR is 0.75	[redacted]	[redacted]	£77,618	[redacted]
12.	Talquetamab vs teclistamab OS HR is 0.80	[redacted]	[redacted]	£100,501	[redacted]
13.	Talquetamab vs teclistamab OS HR is 0.85	[redacted]	[redacted]	£138,058	[redacted]
14.	Talquetamab vs teclistamab OS HR is 0.90	[redacted]	[redacted]	£211,196	[redacted]

INHB, incremental net health benefit; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation

5.6 Conclusions of the cost effectiveness section

The company's economic analysis was based on a partitioned survival model programmed in Excel. The company's model draws on survival evidence from the MajesTEC-1 trial (teclistamab) by using lognormal models calibrated to clinical expert opinions for OS, PFS and TTD, then assumed proportional hazards based on their ITC of two single-arm studies (MonumenTAL-1 and MajesTEC-1) to obtain survival for talquetamab OS, PFS and TTD. The EAG found that the company's ITC methods are likely to have resulted in potential biases in favour of talquetamab, which transcends to the company's economic model. The key concerns around the company's ITC are:

- The ITC does not appear to consider the impact of COVID-19 upon the survival of the unvaccinated MajesTEC-1 population. This would result in an underestimate of teclistamab survival.
- Regression studies show that the company's ITC OS HR is an outlier and favour talquetamab.
- Real-world studies show that the company's modelling of talquetamab survival appears optimistic while modelling of teclistamab is pessimistic.

The EAG consider the company's approach of using ITC HR applied to calibrated lognormal modelling of teclistamab OS, PFS and TTD further compound biases in favour of talquetamab. The lognormal model of OS, PFS and TTD is not the most appropriate parametric curve for a proportional hazards approach.

Another potential bias in favour of talquetamab is IVIg usage not fully/appropriately captured in the company's model. The EAG assumes that IVIg is used to mitigate the effects of infection and is only received by people that are alive. Based on the evidence submitted, it is evident that there will be more IVIg usage in people receiving talquetamab compared to teclistamab over the first 40 months.

We amended the company's economic model based our preferred assumptions, which formed the basis of EAG's base-case model. These changes resulted in differences between the company's and the EAG's base-case results. Both the company's and EAG's results are based on the PAS prices available. Based on our critique, we made the following changes:

- Calibrated Weibull modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS.
- Calibrated Weibull modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS.
- Calibrated Weibull modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD.
- Exclude half-cycle correction.
- Discounting from Year 1 onwards.
- We assumed that the people who received subsequent talquetamab and teclistamab treatment would require IVIg treatment. In the absence of data, we assumed that [redacted] of people who received subsequent talquetamab treatment would require IVIg treatment and [redacted] of people who received subsequent teclistamab treatment would require IVIg treatment.
- Include subsequent talquetamab treatment for a fair comparison of the competing interventions.
- Exclude of AE disutilities.

Using the EAG's preferred assumptions resulted in an ICER of £30,106 per QALY compared to the company's base-case ICER of £29,277 per QALY. There is little difference between the company's and EAG's base-cases. However, given the reservations of the company's ITC HR, and the challenges of re-analysis without IPD, our preference was to undertake scenarios to assess the impact to the ICER by increasing the hazard ratio. Additionally, in the absence of better evidence on IVIg usage and lack of functionality in the model to implement IVIg usage depending on infection rate and proportion alive, the EAG opted for a conservative approach in scenario analysis to assume that IVIg use to be equal in both arms.

The EAG preferred assumptions address some of the concerns raised; however, there are outstanding uncertainties, which should be resolved to understand the true cost-effectiveness of talquetamab compared to teclistamab.

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7 Appendix

7.1 List of company and EAG cost-effectiveness analyses (applying confidential prices)

The EAG undertook analyses of the company's base-case using the available PAS and commercial arrangements that are in place. In the absence of commercial agreements, we maintain list prices in these analyses. The results of those analyses are presented in a separate document. Here we present the analyses undertaken:

The EAG confidential appendix report includes the following analyses:

- Company's cost-effectiveness analysis applying confidential prices for other treatments
    - Deterministic base-case analysis, using the highest MPSC prices
    - Deterministic base-case analysis, using the lowest MPSC prices
    - Deterministic base-case analysis, using the mid-point MPSC prices
    - Probabilistic sensitivity analysis, using the mid-point MPSC prices
    - Company scenario analyses, using the mid-point MPSC prices
    - EAG scenario analyses using the company's model and the mid-point MPSC prices
- EAG cost-effectiveness analysis applying confidential prices for other treatments
    - Deterministic base-case analysis, using the highest MPSC prices
    - Deterministic base-case analysis, using the lowest MPSC prices
    - Deterministic base-case analysis, using the mid-point MPSC prices
    - Probabilistic sensitivity analysis, using the mid-point MPSC prices
    - Scenario analysis results, using EAG's model and the mid-point MPSC prices

7.2 EAG changes to the model

In Table 55, we present the details of the changes made to the company's model that formed the basis of the EAG base-case.

Table 55: EAG changes to the company model

EAG's preferred assumption	Changes made to the company's model
Modelling of OS	Unhide rows in the Clinical Inputs worksheet and select Weibull modelling for teclistamab and talquetamab OS, PFS and TTD
Modelling of PFS	
Modelling of TTD	
Half-cycle correction	Settings worksheet, cell G18, select 'Not applied' from the drop-down box.
Discounting	In the Engine (Talquetamab) worksheet, in column A create Discount cycle [ROUNDDOWN(B21/52,0)] for the model time horizon. In columns AJ, AX and BH, calculate the discount factor. For example, [=1/(1+p_DiscCost)^(@Discount_cycle)]
Additional IVIg treatment	In the Cost Inputs_others worksheet in row 28, create the number of IVIg treatment doses (teclistamab). In the Parameters worksheet, in row 217 adopt the same approach as in row 216 but select the doses that correspond to the initial treatment arm. For talquetamab, select Equal to the initial doses' and for teclistamab, select 2/3 of the initial doses
All-in approach	In the Settings worksheet, cell H11, select 'With OS adjustment -TEC and TAL allowed'
Adverse event disutilities	In the Settings worksheet, cell H53, select 'No' from the dropdown box.
IVIg, intravenous immunoglobulin; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation	

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	TCE adult (≥18 years of age) patients with RRMM diagnosis according to IMWG (i.e., received ≥3 prior treatments including at least one IMiD, PI and anti-CD38 mAb)
Experimental intervention	Talquetamab monotherapy
Comparator	Teclistamab monotherapy
Outcomes	ORR, VGPR, CR, DOR, PFS, and OS

List the confounding domains relevant to all or most studies

EMD, number of prior lines, haemoglobin, non-IgG MM, EMD), ISS stage, or male gender

List co-interventions that could be different between intervention groups and that could impact on outcomes

N/A

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	TCE adult (≥18 years of age) patients with RRMM diagnosis according to IMWG (i.e., received ≥3 prior treatments including at least one IMiD, PI and anti-CD38 mAb)
Experimental intervention	Talquetamab monotherapy
Comparator	Teclistamab monotherapy

Is your aim for this study…?

- ✕ to assess the effect of *assignment to* intervention
- ☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

ORR, VGPR, CR, DOR, PFS, and OS

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	Description	EAG assessment of ORR, PFS, and OS
1. Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Although the company used the IPTW method to adjust for 17 baseline (prognostic) covariates, there still remains a potential for residual confounding due to unmeasured/unknown confounders.	Y
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	Patients were followed up from the initiation of their treatment until progression, death, lost to follow-up, or DCO. Follow up time was not split according to intervention received. However, after progression, patients in both arms were switched to other subsequent treatments (available or not available in UK) and the company used a two-stage method and the secondary baseline accelerated failure time model to calculate counterfactual survival times to adjust for switching to subsequent treatments by removing the effects of non-UK treatments.	Y
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	It is likely that progression/discontinuation of the initial treatment before switching to subsequent treatment was not independent and switching was related to some prognostic variable which was related to the prognosis. In other words, patients with poor prognosis are likely to progress and then discontinue or switch to other treatment. Unaccounted time-dependent confounders may have biased the results.	PY

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	The company used the IPTW method to adjust for 17 baseline covariates.	Y
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	The covariates were identified by clinical experts and the regression analyses that determined the associations between these covariates and the ITC outcomes (OS, PFS). The potential for unmeasured and unknown confounding effects still remain.	PY
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No mediating variables were controlled for by the company.	N
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Confounding domains were generally reliably measured, and the adjustment method was appropriately chosen and conducted. The potential for unmeasured/unknown or time-dependent confounding effects still remains.	PN
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Both studies MajesTEC-1 and MonumenTAL-1 measured and reported the variables that were controlled for in the ITC.	Y
	the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well performed randomized trial due to potential for some confounding.	**Moderate**
Risk of bias judgement		
Optional: What is the predicted direction of bias due to confounding?	-	Unpredictable

2. Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Participants were selected based on a prespecified selection criterion, which did not include characteristics observed after treatment initiation.	N
2.4. Do start of follow-up and start of intervention coincide for most participants?	Both MajesTEC-1 and MonumenTAL-1 are single-arm open-label multicenter clinical trials with strict follow-up protocols. Patients were likely to be followed up from the assignment or start of their therapy	Y
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA	NA
Risk of bias judgement	All or most eligible participants were included in the studies, and start of follow ups coincided with start of the interventions	**Low**
Optional: What is the predicted direction of bias due to selection of participants into the study?	-	Unpredictable

3. Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	The relevant interventions were pre-specified with details such as dose and frequency. Treatment doses were in accordance with NICE recommendations and the marketing authorisations.	Y
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Both MajesTEC-1 and MonumenTAL-1 are single-arm open-label multicenter clinical trials with protocols including strict definitions of intervention start, dose, frequency.	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Both MajesTEC-1 and MonumenTAL-1 IPD were collected prospectively, meaning that the outcome knowledge could not have influenced the treatment assignment.	N
Risk of bias judgement	The intervention definition and assignment preceded the outcome ascertainment . It is unlikely that the knowledge of outcome influenced the intervention assignment.	**Low**
Optional: What is the predicted direction of bias due to classification of interventions?	-	Unpredictable

4. Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Patients received intervention as part of routine care, therefore deviations beyond those expected in usual practice are not expected. Given the similarity in the protocols and study design, the extent of care between MajesTEC-1 and MonumenTAL-1 trials is not expected to be systematically different. Also, the knowledge of treatment to influence to switch to a better treatment is not applicable as the trials were single-arm. The proportion of major treatment-related protocol deviation was low 9.1% in MajesTEC-1 and 7.1% in MonumenTAL-1 trials.	N
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	-	NA
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?	-	NA
4.4. Was the intervention implemented successfully for most participants?	-	NA
4.5. Did study participants adhere to the assigned intervention regimen?	-	NA
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	NA
Risk of bias judgement	Any potential deviation from intervention would reflect usual practice. There were no important protocol deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome.	**Low**
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	-	Unpredictable

5. Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Outcome data were available for all or most of the patients but some baseline characteristics were missing for some patients below 2%, and cytogenetic profile was missing for 10-13% patients.	PY
5.2 Were participants excluded due to missing data on intervention status?	Participants with missing data were not excluded. Imputation was performed for missing values in MajesTEC-1 IPD (4.2% withdrew from the study). For MonumenTAL-1 trial no imputation was performed and a separate category "Missing" was created to describe the proportion of missing values (3.4% lost to follow-up). It is unlikely to have a substantial difference in missing values between MajesTEC-1 IPD and MonumenTAL-1 IPD.	PN
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	See above	PN
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	-	NA
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	-	NA
Risk of bias judgement	All patients had outcome data reported and no patients were excluded from the analysis based on missing data. Efficacy analyses included all 154 participants in the All Treated Analysis Set of the MajesTEC-1 IPD and all 165 patients in MonumenTAL-1 trial IPD.	**Low**
Optional: What is the predicted direction of bias due to missing data?		Unpredictable

6. Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Although both IPD sets came from open-label trials (MajesTEC-1 and MonumenTAL-1), the knowledge of intervention assignment would have a negligible effect on the measurement of outcomes, which were objective in nature (ORR, PFS, DOR, OS).	N
6.2 Were outcome assessors aware of the intervention received by study participants?	Outcome assessors were aware of the intervention status. However, the outcomes which are objective involve negligible or no assessor judgement.	Y
6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes, the methods for outcome assessment were prespecified and comparable between the IPDs of two trials given the same TCE RRMM population and use of bispecific monoclonal antibodies (talquetamab and teclistamab) as experimental treatments, and the same company.	Y
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Not expected, see the explanation above	PN
Risk of bias judgement	All ITC outcomes are objective and unlikely to influence assessor's judgement.	**Low**
Optional: What is the predicted direction of bias due to measurement of outcomes?	The knowledge of the treatment may overestimate the assessed outcome if it is of subjective nature.	Favours experimental

7. Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1. ... multiple outcome *measurements* within the outcome domain?	Some outcomes (TTR, TTD, TTNT, and MRD rate) measured in MajesTEC-1 and MonumenTAL-1 trials and specified in the NICE scope's decision problem, are not reported in the ITC analysis results section. This may be a potential for selective reporting bias.	PY
7.2 ... multiple *analyses* of the intervention-outcome relationship?	No additional analyses were conducted	PN
7.3 ... different *subgroups*?	No subgroup analysis conducted	N
Risk of bias judgement		**Moderate**
Optional: What is the predicted direction of bias due to selection of the reported result?	Reporting only selected outcomes with significant differences in favor of the experimental treatment will overestimate an overall beneficial effect of treatment.	Favours experimental

Overall bias		
Risk of bias judgement	Risk of bias was judged to be low for 5/7 domains of bias. Two domains (2/7) of "Confounding" and "Bias in selection of the reported result" were judged to be at moderate risk of bias. The ITC analysis study therefore is judged to be at overall "Moderate" risk of bias.	**Moderate**
Optional: What is the overall predicted direction of bias for this outcome?	-	Unpredictable

Y='yes'; PY='probably yes'; PN='probably no'; N='no'; N/A=not applicable; NICE=National Institute for Health and Care Excellence; OS=overall survival; ROBINS-I=Risk Of Bias In Non-randomized Studies of Interventions; TCE RRMM=triple-class exposed relapsed refractory multiple myeloma; TTNT=time to next treatment; TTR=time to response; TTD=time to treatment discontinuation; MRD=minimal residual disease; IPD=individual patient data; DOR=duration of response; ORR=overall response rate; PFS=progression free survival

Analysis in the cPAS appendix

List of company and EAG cost-effectiveness analyses (applying confidential prices) and source of prices

The EAG undertook analyses of the company's base-case analysis using the available PAS and commercial arrangement that are in place. In the absence of commercial agreements, we maintain list prices in these analyses. The results of those analyses are presented in a separate document. Here we present the analyses undertaken:

The EAG confidential appendix report includes the following analyses:

- Company's cost-effectiveness analysis applying confidential prices for other treatments
    - Deterministic base-case analysis, using the highest MPSC prices
    - Deterministic base-case analysis, using the lowest MPSC prices
    - Deterministic base-case analysis, using the mid-point MPSC prices
    - Probabilistic sensitivity analysis, using the mid-point MPSC prices
    - Company scenario analyses, using the mid-point MPSC prices
    - EAG scenario analyses using the company's model and the mid-point MPSC prices
- EAG cost-effectiveness analysis applying confidential prices for other treatments
    - Deterministic base-case analysis, using the highest MPSC prices
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    - Deterministic base-case analysis, using the mid-point MPSC prices
    - Probabilistic sensitivity analysis, using the mid-point MPSC prices
    - Scenario analysis results, using EAG's model and the mid-point MPSC prices

Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) England (2025)

Publication date: March 2025 version number: 2.0

Commissioning position

Summary

Therapeutic immunoglobulin is recommended to be available as a routinely commissioned treatment option for the indications within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

Plain language summary

About the treatment

Immunoglobulin replacement therapy is a blood-based treatment. Immunoglobulin is made from plasma separated out from donated blood. During manufacture everything except a type of immunoglobulin called immunoglobulin G (IgG) is removed from the plasma. The immunoglobulin contains IgG antibodies that help to fight infection. Therapeutic immunoglobulin is used when the immune system is either not making antibodies, not making enough antibodies or the ones they are making do not work properly. IgG has other effects too, so it is not just used for people with immune deficiency. You might hear about immunoglobulin being used in some people with other immune (autoimmune) problems. Immunoglobulin can be given intravenously (into a vein) or subcutaneously (under the skin).

What we have decided

NHS England has carefully reviewed the evidence to treat the indications within this policy (detailed in appendix A) with therapeutic immunoglobulin. We have concluded that there is enough evidence to make the treatment available at this time.

Indications that have been considered as part of the evidence review and determined to be "not routinely commissioned" are included in Appendix B. This list is not exhaustive and

therefore any indication not explicitly detailed within this policy is considered to be “not routinely commissioned”.

Links and updates to other policies

This document updates and replaces:

- Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2024
- Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021
- Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England November 2019 v1.4
- Department of Health and Social Care. Clinical Guidelines for Immunoglobulin Use (2nd edition update; July 2011): *dh_131107.pdf (publishing.service.gov.uk)*

Committee discussion

The Clinical Priorities Advisory Group reviewed the evidence and recommended the policy proposition cpag-commissioning-criteria-policy-for-therapeutic-immunoglobulin-2021.pdf (england.nhs.uk).

The condition

The policy covers multiple indications, detailed in Appendix A, for immunology, haematology, neurology, infectious diseases and other specialities.

Evidence summary

The updated commissioning criteria for the use of therapeutic immunoglobulin (Ig) 2024 describes all conditions for which Ig is commissioned and provides the detail around the role, dose and place of Ig in the treatment pathway for individual indications alongside possible alternative treatment options for use of Ig in both adults and children. This policy was built on a review of the literature including detailed scoping reviews undertaken by Cochrane Response (2020) updated with a further evidence review, expert opinion and multi-organisational input. The commissioning criteria were developed by the Ig Expert Working Group following wide consultation with specialty experts, relevant scientific societies and the NHS England Specialised Commissioning Clinical Reference Groups (CRGs).

Implementation

The Immunology and Allergy CRG, in conjunction with the Ig Oversight Group, will review this document as per NHS England policy review process or when there is a significant change in evidence. Recommendations on Ig dose and outcomes are based on a combination of available evidence and expert opinion.

Criteria

The following commissioning criteria set out all the indications recognised by NHS England as immunoglobulin responsive based on a systematic literature review. These were previously categorised in a hierarchy of importance in a Demand Management Plan as follows:

- Red indications - conditions for which Ig treatment is considered the highest priority because of a risk to life without treatment
- Blue indications - conditions for which there is a reasonable evidence base for the use of Ig but other treatment options are available
- Grey indications - immune-mediated disorders with limited or little/no evidence
- Indications for which immunoglobulin is not recommended.

With this policy update, the colour coding system is removed and indications are instead categorised as follows:

- Routinely commissioned indications – see Appendix A
- Not routinely commissioned indications - see Appendix B

The Demand Management Plan will be superseded by the Immunoglobulin Management Plan once published.

Application process:
A completed (e-) referral form is required for use of Ig in ALL indications to ensure immunoglobulin stewardship and oversight by the Sub-Regional Immunoglobulin Assessment panels (SRIAP). For the purpose of this document, the term 'panel' refers to SRIAP.

Local policy should be followed for all applications – urgent, non-urgent and out-of-hours. Consideration needs to be given to the requirement of panel approval and oversight as follows:

- Prior panel approval required – NO
  Treatment can proceed without prior panel approval. Submit a completed application form for retrospective review by the panel
- Prior panel approval required – YES
  Treatment should not proceed without prior panel approval. For urgent approvals in hours – a process will need to be in place on the agreed pathway for approval. For those cases that require out of hours approval, panels will have local processes in place, to ensure robust governance for retrospective panel approval. Where local expertise is not available, panels will also be able to advise on dose optimisation and trials of treatment withdrawal. If prior panel approval is not possible, for example in an urgent case, retrospective approval must be sought.

All referrals should be carried out via the Medicine Database Solutions and Services (MDSAS) National Immunoglobulin Database e-referral platform. Immunoglobulin data will be reviewed and findings reported to the Immunoglobulin Oversight Group and relevant CRG to inform any recommendations on changes in policy. If available, MDSAS data will be analysed for ethnic groups to ensure any possible inequality in access is identified.

Indications or clinical scenarios not listed in appendix A of this document are not routinely commissioned and require an Individual Funding Request (IFR) application to be submitted to the NHS England IFR system, should the clinician consider there is an arguable case for the IFR policy criteria to be met. If the IFR is approved, the diagnosis and locally agreed efficacy criteria are recorded on the immunoglobulin database.

More information on IFRs in general is available here: *NHS commissioning » Key documents (england.nhs.uk)*.

Dosing in adult patients:

In keeping with the advice included in previous iterations of these guidelines and to ensure cost-effective use and minimise dose-dependent adverse effects, Ig prescribing will be based

on ideal body weight dosing (IBW)[1,2] with doses subsequently titrated according to clinically meaningful response (immunomodulation) or Ig trough level (immunoreplacement).

For pregnant patients, IBW based on booking weight should be used.

Optimal use of vials:

The following principles should apply:

- Calculate total treatment course and round down to the nearest dose which can be administered using whole vials.
- Note in an adult patient part vials should never be used. Where the dose is split over multiple days, daily dose may differ.

Example:

- Male patient - Height 170cm; Actual Body Weight (ABW) 84kg
- Diagnosed with Guillain-Barre syndrome and meets criteria for IVIg, plan to receive 2g/kg based on IBW to be given over 5 days as per guidelines.

Calculation of IBW (male)	IBW = 50 + (0.91 x [Height(cm) – 152.4]) = 50 + (0.91 x [170-152.4]) = 66kg
Calculation of total dose	2 x 66kg = 132g → rounded down to nearest 5g vial = 130g
Split total dose over 5 days	• Day 1: 30g • Day 2: 20g • Day 3: 30g • Day 4: 20g • Day 5: 30g

Dosing in paediatric patients

In all paediatric patients Ig dosing should be based on IBW. ABW should not be used. In patients whose ABW is < IBW, IBW should still be used to ensure appropriate dosing and preventing underdosing.

The recommended methods suggested by the Royal College of Paediatrics and Child Health (RCPCH) and Neonatal and Paediatric Pharmacy Group (NPPG) to calculate IBW, include the use of the table at the back of the British National Formulary for Children (BNFC)[3] [Approximate Conversions and Units | About | BNFC | NICE] or methods suggested in the

[1] Chow S et al. Transfusion and apheresis science: official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2012;46:349-52.
[2] Grindeland JW et al. Ann Pharmacotherapy. 2020;54:205-212
[3] MedicinesComplete. *BNF for Children*. Available from: *British National Formulary for Children | MedicinesComplete*

UKMI document[4]. In the future, the RCPCH and NPPG aim to work on a standardised approach in conjunction with the BNFC.

Where possible doses should be rounded down to the nearest vial size to prevent wastage.

[4] Specialist Pharmacy Service. *UKMI NPPG - drug dosing in childhood obesity May 2021*. Available from: *How should medicines be dosed in children who are obese? – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice*

Appendix A

Use of Immunoglobulin in Immunology

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Haematopoeitic stem cell transplantation (HSCT) in primary immunodeficiencies (PID) / inborn errors of immunity (IEI) – long term use	PID (IEI) patients undergoing HSCT	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dosing requirements may increase and should be based on clinical outcome. Because of the possibility of B-cell reconstitution, evaluation of immune function (off Ig) is required at 2 years	• Raised trough IgG level compared to baseline	No
Primary immunodeficiencies (PID) / Inborn errors of immunity (IEI) associated with significant antibody defects (excluding specific antibody deficiency) – long term use	A specific PID (IEI) diagnosis must be established by a clinical immunologist In newly diagnosed patients with PID (IEI) with no significant burden of infection, the decision to start Ig replacement should be based on an MDT discussion	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	• Raised trough IgG level compared to baseline • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	No
Specific antibody deficiency – long term use	• Diagnosis by a clinical immunologist • Severe, persistent, opportunistic or recurrent bacterial infections despite continuous oral antibiotic therapy for 6 months • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	None, but see comments in column of position of Ig	Many patients with specific antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective	Initiate trial at 0.4 – 0.6 g/kg/month for a period of 6 - 12 months; Long-term maintenance treatment should be based on clear evidence of benefit from this trial and require panel approval. Dose requirements may increase and should be based on clinical outcome	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	Yes
Secondary antibody deficiency – long term use	• Underlying cause of hypogammaglobinaemia cannot be reversed, or reversal is contraindicated; **OR** Hypogammaglobinaemia associated with drugs including emerging bispecifics, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20, CD19 agents, daratumumab etc) post-HSCT*, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist **AND** • (a) Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months	None, but see comments in column of position of Ig	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective Since infection susceptibility in patients with haematological malignancies is frequently multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason, annual reviews of treatment are	0.4 – 0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	(b) IgG <4 g/L* (excluding paraprotein) (c) Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge **Note:** It is recognised that vaccine challenge may be of limited value in patients with very low serum IgG (< 3g/L). In these circumstances, vaccine challenge may be omitted if it is considered inappropriate clinically • It is acknowledged that not all of criteria (a) – (c) will need to be fulfilled for an individual patient * IgG < 4g/L – not specific for paediatric patients • In patients developing **hypogammaglobinaemia associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells)** targeted against B cell or plasma cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate • Use of **Ig post-CAR-T therapy in B-cell acute lymphoblastic leukaemia (B-ALL)** Because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR-T cell therapy. As with the use of Ig post-CAR-T therapy in B-cell lymphoma, continued use of IVIg should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection • Use of **Ig post-CAR-T cell therapy in B-cell lymphoma**		recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer			

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	The need for Ig replacement in patients receiving CAR-T cell therapy for B-cell lymphoma is variable ranging between 31% to 64% in published studies[5] highlighting faster B-cell recovery in this group in contrast to patients with B-cell acute lymphoblastic leukaemia • Use of Ig at inception of bi-specific antibody treatment in patients with myeloma and B-cell lymphoma Many patients in these disease groups will have a low serum IgG at baseline due to previous chemo-immunotherapy, including CD20 and CD38 depleting agents. The prophylactic use of Ig would be appropriate in patients with a serum IgG of < 4g/l at the time of commencement of a bi-specific antibody. *There is variable practice regarding Ig replacement in adult patients with hypogammaglobinaemia post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows: 'Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level'[6]. It is possible that patients with recurrent sino-pulmonary infections on a background of chronic pulmonary GVHD and hypogammaglobinaemia may benefit if they fulfil the criteria for secondary antibody deficiency.					
Thymoma with immunodeficiency – long term use	• Profound B cell depletion **AND/OR** • significant antibody deficiency	None	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4 – 0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	• Raised through IgG level compared to baseline • Reduction in number of infections • Reduction in number of treatment courses of antibiotics • Reduction in number of days in hospital.	No

[5] Locke et al. Lancet Oncol 2020; 20:31-42, Wang et al NEJM 2020;382:1331-42, Schuster et al NEJM 2017;377:2545-54

[6] Bhella et al. Biol Blood Marrow Transplant 2018;24:909-13

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Acquired red cell aplasia associated with chronic parvovirus B19 infection – short term use	• Parvovirus B19 infection confirmed by PCR, **AND** • Evidence of high viral load, usually above 10^9 IU/ml In cases of foetal hydrops: Likely to be associated with parvovirus B19	Infection other than parvovirus B19	Ig is an adjunct to transfusion. Chronic parvovirus infection generally occurs on a background of immunosuppressive therapy, primary or HIV-related immunodeficiency and may resolve with a reduction in immunosuppression. Acute parvovirus infection associated with transient aplastic crisis requires urgent transfusion rather than Ig	1.0 – 1.2 g/kg in divided doses. This may be repeated on relapse and for a 2nd relapse	• Rise in haemoglobin • Rise in reticulocyte count • Transfusion independence	Yes
Alloimmune thrombocytopenia (foetal-maternal/neonatal) **Foetal-maternal alloimmune thrombocytopenia (FMAIT)**	**Prevention or treatment of foetal thrombocytopenia or haemorrhage:** • Clinical suspicion of FMAIT in the antenatal setting based on clinical and laboratory features: Unexplained previous foetal death, haemorrhage, hydrocephalus or thrombocytopenia or known affected sibling, **AND** • The presence of maternal platelet-specific alloantibodies directed against current paternal antigens (most commonly HPA-1a or HPA-5b).	None	**Maternal:** Ig is the primary treatment and sometimes combined with steroids	**Maternal:** The dose of Ig and the gestation at which to start treatment should be tailored according to the history of NAIT in earlier pregnancies. A patient with a low-risk obstetric history (where the previous infant had thrombocytopenia but no intracranial haemorrhage) should be commenced on 0.5-1.0 g/kg/week from 20 weeks' gestation. In high-risk pregnancies, treatment should commence from as early as 12 weeks' gestation with a dose of 1 g/kg/week (where the previous foetus or neonate had intracranial haemorrhage after 28 weeks' gestation), or 2 g/kg/week (where the previous foetus or neonate had intracranial haemorrhage before 28 weeks)[7,8,9,10,11] The weight used to calculate the dose will be the mother's weight at booking.	• Successful outcome of pregnancy i.e. no severe haemorrhage such as intracranial haemorrhage • Platelet count above $50x10^9$/L at time of delivery • Increment in neonatal platelet count	Yes – for FMAIT

[7] Pacheco et al. Fetal and neonatal alloimmune thrombocytopenia. Obst & Gyn 2011; 118: 1157-1163
[8] Peterson et al. Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management. Br J Haematol. 2013; 161: 3-14
[9] Regan et al. Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT). BJOG 2019; 126: 173-185.
[10] Lieberman et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. Br J Haematol. 2019; 185: 549-562
[11] Winkelhorst et al. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Exp Rev Hematol 2017; 10: 729-737

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Neonatal alloimmune thrombocytopenia (NAIT)	**Prevention or treatment of neonatal thrombocytopenia or haemorrhage:** Clinical suspicion of NAIT in the neonatal setting based on clinical features suggestive of bleeding e.g. purpura and/or bruising and/or more serious bleeding and a low platelet count		**Neonatal:** First line treatment is with HPA-1a/5b – negative platelets which covers 95% of HPA incompatibilities responsible for NAIT. Platelet transfusion is effective immediately. In contrast, Ig is a second line treatment and works in approximately 75% of cases. It has a delayed effect over 24 – 48 hours. Ig may be of value if there is prolonged thrombocytopenia with the aim of minimising the need for platelet transfusions	**Neonatal:** 1 g/kg; a 2nd dose may be required if thrombocytopenia persists In the rare event of retreatment after the 2nd dose, approval from SRIAPs should be sought.		No – for NAIT
Autoimmune haemolytic anaemia (AHA, including Evans syndrome) – short term use	• Symptomatic or severe anaemia, except in patients with co-morbidities), **AND** • Refractory to conventional treatment with corticosteroids, **OR** Corticosteroids contra-indicated, **OR** As a temporising measure prior to splenectomy **AHA in pregnancy:** • Pregnant women with warm AHA refractory to corticosteroids **OR** with evidence of foetal anaemia. • Neonates of mothers with AHA who have evidence of haemolysis **AND** rising bilirubin despite intensive phototherapy	None	Ig is reserved for patients unresponsive to steroids or where steroids are contra-indicated	1 - 2 g/kg in 2 to 5 divided doses. This may be repeated on relapse and for a 2nd relapse. The weight used to calculate the dose will be the mother's weight at booking.	• Rise in haemoglobin • Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) • Transfusion independence	No – for treatment of acute episodes Yes – for repeat courses
Coagulation factor inhibitor disorder (alloantibodies and autoantibodies) – Acquired von Willebrand disease (VWD) – short term use	• Life- or limb-threatening haemorrhage, **AND** • Failure to respond to other treatments, **AND/OR** • Prior to invasive procedure Treatment directed by the haemophilia centre at which the patient is registered	Acquired VWD associated with IgM monoclonal gammopathy	Ig is a therapeutic option in acquired VWD, particularly in cases associated with an IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF-containing concentrates and recombinant Factor VII	Either 0.4 g/kg for 5 days or 1 g/kg for 2 days	• Rise of factor level • Resolution of bleeding • Reduction in number of bleeding episodes	Yes If prior approval is not possible then treatment should proceed, and retrospective approval should be sought

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Haemolytic disease of the newborn – short term use	Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease: • Rising bilirubin despite intensive phototherapy (see NICE CG98[12]) Prevention of foetal haemolytic disease in women with a previous history of this and confirmed red cell antibodies to current paternal or foetal antigens, to delay the need for intrauterine transfusions	None	Ig is an adjunct to phototherapy See NICE CG98[12]	0.5 g/kg over 4 hours	• Reduction in bilirubin level • Reduced need for exchange transfusion • Long term morbidity	No
Haemophagocytic syndrome (Haemophagocytic lymphohistiocytosis or HLH) – short term use	Diagnosis by a consultant haematologist or rheumatologist based on H-score* including: • pyrexia • organomegaly • multiple lineage cytopenias • triglycerides • fibrinogen • ferritin • serum aspartate aminotransferase • haemophagocytosis on bone marrow biopsy • long-term pharmacological immunosuppression *A score >169 is 93% sensitive and 86% specific for HLH	None	Other therapies include IL-1 receptor inhibition (anakinra) See NHS England Clinical Commissioning Policy[13]	2 g/kg in 2 - 5 divided doses alongside corticosteroids (dexamethasone) as per HLH protocol. This may be repeated on relapse and for a 2nd relapse, where alternative therapies are not indicated or are contraindicated	• Improvement of cytopenias • Improvement of HLH markers – Ferritin/soluble CD25 • Survival	Yes

[12] National Institute for Health and Care Excellence. Jaundice in newborn babies under 28 days. Clinical guideline [CG98]. Available from: https://www.nice.org.uk/guidance/cg98

[13] National Health Service. Clinical Commissioning Policy: Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages [210701P] (1924). Available from: https://www.england.nhs.uk/publication/anakinra-for-haemophagocytic-lymphohistiocytosis-for-adults-and-children-in-all-ages

<table>
<tr><th>Indications</th><th>Eligibility criteria</th><th>Exclusion criteria</th><th>Position of immunoglobulin, taking into account alternative therapies</th><th>Recommended dose</th><th>Outcome measures (to be recorded on the national immunoglobulin database)</th><th>Prior panel approval required</th></tr>
<tr>
<td>Immune Thrombocytopenic Purpura (ITP)
- short term use</td>
<td>Ig generally used in only 4 situations in ITP:
1) Life-threatening bleeding
2) Where an immediate increase in platelet count is required e.g. before emergency surgery or other procedure (see table for target platelet counts)
3) Where the patient is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2-3 weeks during a period where other second line treatments are being tried
4) Moderate severity bleeding in patient at higher risk of subsequent severe bleed. Patients with mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding are at higher risk of a subsequent severe bleed

These eligibility criteria are also applicable when considering the short term use of Ig in patients with chronic ITP experiencing acute bleeding or requiring invasive procedures.

Bleeding severity as defined by the “Updated international consensus report on the investigation and management of primary immune thrombocytopenia 2019”[14]

Target platelet counts for surgery*
<table>
<tr><th>Procedure</th><th>Platelet count</th></tr>
<tr><td>Dentistry</td><td>>20</td></tr>
<tr><td>Simple dental extraction</td><td>>30</td></tr>
<tr><td>Complex dental extraction</td><td>>50</td></tr>
<tr><td>Regional dental block</td><td>>30</td></tr>
<tr><td>Minor surgery</td><td>>50</td></tr>
<tr><td>Major surgery</td><td>>80</td></tr>
<tr><td>Major neurosurgery</td><td>>100</td></tr>
</table>
</td>
<td>None</td>
<td>Thrombopoietin mimetics may be useful substitutes in some patients (in situation 3) or as an adjunct in the other situations</td>
<td>Adults: 1 g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding:
e.g. intracranial bleed or pulmonary haemorrhage.
Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1 g/kg) may be considered at day 5- 7

Children: 0.8 – 1.0 g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding, such as an intracranial bleed or pulmonary haemorrhage.
Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1 g/kg) may be considered at day 5 - 7</td>
<td>• Increase in platelet count
• Resolution of bleeding
• Reduction in number of bleeding complications</td>
<td>No - for acute ITP; the use of a 2nd dose should be discussed with the designated panel lead.

Yes – for maintenance treatment</td>
</tr>
</table>

[14] Provan et al. Blood Adv (2019) 3 (22): 3780–3817

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	ITP in pregnancy: Maintenance treatment with Ig may be required antenatally to maintain platelets above $20x10^9$/l and/or to increase platelets to over 50 $x10^9$/l for delivery in women with symptomatic persistent or chronic ITP where other treatments have failed *There is controversy regarding the target platelet count for epidural anaesthesia[15]. There are no data to support a minimum platelet count and each case must be carefully considered. In the absence of bruising, bleeding history, and anticoagulation and if the INR, APTT and fibrinogen levels are normal, a small consensus of obstetric anaesthetists agree no changes to normal practice are needed until the platelet count drops below 50.					
Covid vaccine-induced thrombosis and thrombocytopenia (VITT) or a syndrome of anti-PF4 (platelet factor 4) associated immune-mediated thrombosis and thrombocytopenia	Confirmed/Probable diagnosis of VITT made by a haematologist conforming to up to date guidance from the Expert Haematology Panel - See British Society for Haematology website for details.	Isolated thrombocytopenia or thrombosis: • Reduced platelet count without thrombosis with D-dimer at or near normal and normal fibrinogen. • Thrombosis with normal platelet count and D dimer	Treatment with intravenous Ig irrespective of the degree of thrombocytopenia is urgent as this is the treatment most likely to influence the disease process. A repeat course of IVIg may be required depending on clinical course	1 g/kg (divided over 2 days if required)[16]	• Increase in platelet count	No
Post-transfusion hyperhaemolysis – short term use	Treatment of acute post-transfusion hyperhaemolysis	None	In combination with steroids, Ig is used as 1st line treatment	2 g/kg (usually over 2 days) given with IV methylprednisolone	• Rise in haemoglobin • Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) • Transfusion independence • No haemolysis • Maintenance of post-transfusion Hb at 1 – 3 weeks • Avoidance of need for repeated transfusion	No
Prevention of haemolysis in	Symptomatic or severe anaemia (Hb <60g/L, with evidence of on-going			1 - 2 g/kg over 2 - 5 days given with steroids		

[15] Provan et al. Blood 2010;115:168-186
[16] Misbah et al J Clin Path 2023;76:143-144

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
patients with a history of transfusion-associated hyperhaemolysis **Prevention of delayed haemolytic transfusion reaction**	intravascular haemolysis due to a delayed haemolytic transfusion/hyperhaemolysis). It is recognised that some patients with an Hb 60 g/l may require treatment. Patients who have had previous delayed haemolytic transfusion reactions/post-transfusion hyperhaemolysis or who have single or multiple allo-antibodies **AND** who may require a blood transfusion		Eculizumab is commissioned as a 2nd line treatment where 1st line treatment has failed; Rituximab is recommended as a 3rd line treatment[17].	1 – 2 g/kg over 2 - 5 days, given with IV methylprednisolone		
Post-transfusion purpura – short term use	• Sudden severe thrombocytopenia 5 to 10 days post-transfusion of blood products, **AND** • Active bleeding (typically occurs in Caucasian HPA-1a antigen negative females previously exposed to HPA-1a antigen in pregnancy or transfusion)	None	There are now very few cases in UK following the implementation of universal leucocyte-reduction of blood components in 1999	1 – 2 g/kg in divided doses over 2 - 5 days	• Increase in platelet count • Resolution of bleeding • Number of bleeding complications	No

[17] National Health Service. Clinical Commissioning Policy; Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies [URN 1821] [200602P]. Available from: *NHS England » Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies*

Use of Immunoglobulin in Neurology

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Acute idiopathic/ autoimmune dysautonomia/ ganglionopathy	• Acute onset autonomic failure with presence of ganglionic (alpha3) acetylcholine receptor antibodies **OR** Acute onset autonomic failure with clinical pattern consistent with above including pupillary involvement but without identifiable antibodies **AND** • Authorised by specialist autonomic unit	Non-immune causes of autonomic failure (for example primary autonomic failure [PAF] without pupillary involvement, multisystem atrophy [MSA], diabetes mellitus)	Ig may be required to obtain rapid control, but may be substituted by prednisolone, mycophenolate mofetil, plasma exchange or other immunosuppressants which are preferable in the longer term	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability Annual reassessment with Ig suspension as necessary	• Postural BP drop - reduction with improved activities of daily living • Increase in time to significant postural BP drop • Reduction in numbers of syncopal and pre-syncopal episodes • Reduced oral dryness score • Reduced diarrhoea and constipation frequency	Yes
Autoimmune encephalitides (AIE) - antibody associated	• Non-infective encephalitis, with or without underlying teratoma or malignancy with known encephalitis associated antibody (e.g. LGI1, Caspr2, NMDAR, GAD, DPPX, AMPA, GABAb and others) **AND** • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae	Infective encephalitis or other non-inflammatory cause of encephalopathy or seizures	Search for underlying malignancy and treat as appropriate Prednisolone/ methylprednisolone is 1st line, with or without plasma exchange (where this is available) Ongoing treatment with Ig may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is available[18]. Consider recruitment within the trial for suitable patients.	2 g/kg over 5 days initially repeated at 3 - 6 weeks. Repeat course 3 times if necessary. If repeated courses are required, consider institution of alternative longer-term strategy immediately	• Decrease in antibody titre • Improvement in Modified Rankin Score • Decrease in seizure numbers • Improvement on one or more validated tests of memory or executive tasks • Resolution of MRI signal change (where present) • Resolution of hyponatraemia where present	Yes
Autoimmune encephalitides (AIE) - no known antibody defined	• Non-infective encephalitis, with or without underlying teratoma or malignancy without known encephalitis associated antibody	Infective encephalitis or other non-inflammatory cause of	Search for underlying malignancy and treat as appropriate. Prednisolone is 1st line, with or without	2 g/kg over 5 days initially repeated at 3 - 6 weeks. Repeat course 3 times if necessary	• Improvement in Modified Rankin Score • Decrease in seizure numbers • Improvement on one or more validated tests of memory or executive tasks	Yes

[18] University of Liverpool. Enceph-IG Study - Institute of Infection, Veterinary and Ecological Sciences. Available from: *Enceph-IG Study - Institute of Infection, Veterinary and Ecological Sciences - University of Liverpool*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	AND • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae **AND** • Evidence of inflammatory CNS disorder including active CSF, EEG defined seizures, MRI imaging changes consistent with AIE, known antibodies etc in the absence of infection	encephalopathy or seizures	plasma exchange (where this is available) Ongoing treatment with Ig may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/ rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is available[18]. Consider recruitment within the trial for suitable patients.	If repeated courses are required, consider institution of alternative longer-term strategy immediately	• Resolution of MRI signal change (where present) • Resolution of hyponatraemia where present	
Chronic inflammatory demyelinating polyneuropathy (CIDP) - including IgG or IgA associated paraprotein associated demyelinating neuropathy	• Probable or definite diagnosis of CIDP by a neurologist according to the EAN/PNS Criteria[19] **AND** • Significant functional impairment inhibiting normal daily activities. All patients should have an initial documented assessment after induction dosing and a further assessment after 2-3 doses to demonstrate meaningful functional improvement. Annual withdrawal/clinical reviews should be performed to document on-going need.	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	Ig should not always be considered 1st line treatment for CIDP, although it may be where steroids are contra-indicated and plasma exchange is not available. Where steroids, Ig and plasma exchange are all available Ig would be considered preferable in patients with motor predominant CIDP, rapidly progressive disease where rapid response is required (particularly patients requiring admission to hospital) or where steroids or plasma exchange are contra-indicated. Strong consideration should be given to the early use of steroids or	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each and given over a 4 - 8-week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[20]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[21] **Refer to dose optimisation section below for maintenance**	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures: • MRC score • INCAT sensory sum score • ONLS • Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	Short-term initiation treatment to assess Ig responsiveness – No Long-term treatment - Yes

[19] European Academy of Neurology/Peripheral Nerve Society Guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force — Second Revision. June 2021. Journal of the Peripheral Nervous System 26(2)
[20] Lunn M et al. J Peripher Nerv Syst. 2016 Mar;21(1):33-7.
[21] Hughes R et al. Expert Rev Neurother. 2009 Jun;9(6):789-95.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			plasma exchange in other circumstances			
Guillain-Barre syndrome (GBS) **(includes Bickerstaff's brain stem encephalitis and other GBS variants)**	• Diagnosis of GBS (or variant) in hospital, **AND** • Significant disability (Hughes Grade 4) **OR** Disease progression towards intubation and ventilation **OR** mEGRIS score ≥ 3 **OR** Poor prognosis mEGOS ≥ 4	Patients with mild and/or non-progressive disease not requiring intubation	Patients with Miller-Fisher Syndrome do not usually require Ig and unless associated with GBS overlap with weakness will recover normally Plasma exchange is equally efficacious as Ig in GBS and should be preferentially considered where it is clinically appropriate and easily accessible For those disease indications in children and young adults where IVIg and plasma exchange (PLEX) are equally efficacious, IVIg may be preferentially considered if poor peripheral venou s access or challenges in service delivery preclude the use of PLEX	2 g/kg as soon as possible after the diagnosis is confirmed, given over 5 days. Administration over a shorter time frame not recommended because of fluid and protein overload and pro-coagulant effects. Ig is unlikely to be effective if given more than 4 weeks after the onset of symptoms[22]. Second doses of Ig are not effective in the treatment of GBS and may be associated with real potential harm[23].	None	No
IgM Paraprotein-associated demyelinating neuropathy	• Diagnosis by a neurologist, **AND** • Significant functional impairment inhibiting normal daily activities. **AND** • Other therapies have failed, are contra-indicated or undesirable	Mild disease with non-progressive sensory loss and imbalance does not require treatment	Ig is seldom significantly effective, and response should be reviewed at least every 6 months if there is initial functional improvement. Alternative underlying haematological diagnoses should be considered which may direct treatment, or other therapies such as single agent rituximab (or biosimilars) should be considered. Rituximab is recommended in IgM	An initiation regimen of a maximum 4 g/kg divided into at least 2 courses of 1-2 g/kg each and given over a 4- 8-week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[20]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213]. **Refer to dose optimisation section below for maintenance**	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures • MRC score • INCAT sensory sum score • ONLS • Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	Yes

[22] Hughes R et al. Cochrane Database Syst Rev. 2014 Sep 19;2014(9):CD002063
[23] Lunn M et al. Lancet Neurol. 2021 Apr;20(4):249-251.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			paraproteinaemic demyelinating peripheral neuropathy in adults, in line with NHS England clinical commissioning policy[24].			
Inflammatory Myopathies - Dermatomyositis (DM), Juvenile dermatomyositis (JDM), Polymyositis (PM), Other inflammatory myopathies*	• Diagnosis of myositis by a neurologist, rheumatologist, dermatologist or immunologist **AND** • Patients who have significant muscle weakness; **OR** Dysphagia and have not responded to corticosteroids and other immunosuppressive agents; **OR** DM with refractory skin involvement.	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig *Inclusion body myositis is not routinely commissioned	Where progression is not rapid and in the absence of contra-indications, **steroids** should be considered first. In adult patients (and post-pubescent children through the NHS England Medicines for Children policy[25]) with refractory disease associated with myositis-specific antibodies, **rituximab** (or biosimilar) has been approved as a 2nd line treatment by NHS England[26]. **Abatacept** is recommended in refractory idiopathic inflammatory myopathies (adults and children aged 2 and over), in line with NHS England Clinical Commissioning Policy as a 3rd line treatment[27]. **Ig** would be the 4th line treatment line. Ig is seldom effective in isolation and is best used as an adjunct to immunosuppressive therapy.	An initiation course of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each and given over a 4 - 8-week period, with assessment after dosing. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[202] **Refer to dose optimisation section below for maintenance** The need for maintenance treatment in **resistant juvenile dermatomyositis** should be determined on an individual basis	Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter Clinically meaningful improvement in any three of the following prespecified measures: **DM:** functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC score) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • CDASI • CAT or DAS • FVC • CHAQ to include the childhood score **PM/other inflammatory myopathies:** functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC sumscore) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • HAQ • FVC **Dermatomyositis (juvenile – JDM):** • MMT-8 • CMAS score • CK for baseline and assess how a patient has improved after each infusion or at least after 3 infusions. • PGALs is used to assess how many inflamed or swollen joints a patient has.	Yes

[24] National Health Service. Clinical Commissioning Policy: Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults. Available from: *NHS England » Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults*

[25] National Health Service. Commissioning Medicines for Children in Specialised Services. Available from*:* *NHS England » Commissioning Medicines for Children in Specialised Services*

[26] National Health Service. Clinical Commissioning Policy: Rituximab for the treatment of dermatomyositis and polymyositis (adults). Available from: *Rituximab-for-the-treatment-of-dermatomyositis-and-polymyositis-adults.pdf (england.nhs.uk)*

[27] National Health Service. Clinical Commissioning Policy: Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 and over). Available from: *NHS England » Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 years and over)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			Maintenance treatment with Ig for a prolonged period (usually less than 12 months) may be required in a small minority of patients with inflammatory myositis, as a 3rd line treatment after consideration of rituximab (see comments above). In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be attempted at least annually to establish on-going need for treatment.			
Multifocal Motor Neuropathy (MMN)	• Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; **AND** • Significant functional impairment inhibiting normal daily activities	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	No alternative treatments known	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 - 2 g/kg each, and given over a 4 - 8 week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks[202]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213] **Refer to dose optimisation section below for maintenance** If no significant measurable and functionally meaningful improved in abilities has been achieved after 3 doses Ig should be stopped	Clinically meaningful improvement in any 3 of the following prespecified measures • MRC score • Power score from 7 pre-defined pairs of muscles including 4 most affected muscle groups neuro-physiologically • RODS for MMN • Hand dynamometry • ONLS • 10-m walk (in secs) • Any other validated MMN disability measure	Short-term treatment to assess Ig responsiveness – No Long-term treatment - Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Myasthenia Gravis (MG), includes Lambert-Eaton Myasthenic Syndrome (LEMS)	• Diagnosis of MG or LEMS by a neurologist **AND** • Acute exacerbation (myasthenic crisis) **OR** Weakness requires hospital admission **OR** Prior to surgery and/or thymectomy	No specific exclusion criteria but see General notes regarding prothrombotic risks of Ig	All patients requiring urgent in-patient treatment should receive plasma exchange first if available, including considering transfer to an appropriate neuroscience centre. Ig could follow plasma exchange if required. Where plasma exchange is not available, Ig may be appropriate. In rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression) and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered. A rituximab biosimilar agent is likely to be an equally effective alternative therapy and has been approved by NHS England[28] for this group of patients with resistant myasthenia	In acute exacerbation use plasma exchange first where available. Patients admitted to hospital should receive 1 g/kg in the first instance, only receiving a further 1 g/kg if there is further deterioration or no response. Patients with life threatening disease (ITU with respiratory and/ or bulbar failure) should receive 2 g/kg over 2 - 5 days. **Refer to dose optimisation section below for maintenance**	Clinically meaningful improvement in variation of myasthenic muscular strength and fatigue measures by the QMGS MG composite score. Additional efficacy may be monitored using: • Forward arm abduction time (up to 5 min) • Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of another myasthenic muscular score • Dysphagia score • Dysarthria 1-50 counting • Diplopia or ptosis measurement	Myasthenic crisis – No Long-term treatment - Yes
Neuromyotonia (Isaacs syndrome)	• Neuromyotonia from peripheral nerve hyperexcitability associated with significant disability **AND** • Supported by diagnostic electrophysiological changes with or without antibodies to the VGKCh complex (Caspr) and resistant to alternative agents	Non autoimmune myotonia syndromes	Anticonvulsants should be tried first from phenytoin, carbamazepine, sodium valproate and lamotrigine. Immunomodulation: Prednisolone +/- azathioprine or oral immunosuppressant Plasma exchange	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to stability	Clinically meaningful improvement in • Timed up and go walk • Functional measure: e.g. Myotonia Behaviour Scale (MBS), Rivermead Mobility Index, or Brief Pain Inventory • Neurophysiological myotonia assessment	Yes

[28] National Health Service. Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Available from: *Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf (england.nhs.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Non-MS CNS inflammatory disease covering the clinical phenotype of Aquaporin-4 antibodies (AQP4 ab) disease, Neuromyelitis Optica Spectrum Disorder (NMOSD), Acute Disseminated Encephalomyelitis (ADEM) (with or without encephalopathy, including brainstem attacks), Myelin Oligodendrocyte Antibody Disease (MOGAD), Transverse Myelitis (TM), Optic Neuritis (ON)						
Acute disease: Short term use **Chronic relapse prevention:**	• Acute disease attack* not responding to IV methylprednisolone (5 – 7 g or equivalent in children) and plasma exchange. When plasma exchange is not available or delayed or contraindicated, Ig can be used before plasma exchange **AND** • Evidence of ongoing inflammation **AND** • Within 6 weeks unless evidence of active inflammation	Mild relapses without: new neurological signs OR reduced activities of daily living OR other inflammatory disease diagnoses (e.g. MS Sarcoid, Behcets etc)	Refractory to IV methylprednisolone OR plasma exchange not available or contraindicated OR refractory to plasma exchange in cases of severe disability and ongoing inflammation (usually within 6 weeks)	2 g/kg over 2 - 5 days	Clinically meaningful improvement in disease features including 3 of: • Modified Rankin score • 10m walk • 9-hole peg test • Validated neuropsychometric testing • Other relevant validated scale • Objective relevant imaging **Optic neuritis** Clinically meaningful improvement in visual acuity **Transverse myelitis** Clinically meaningful improvement in • EDMUS **OR** • ASIA	No
MOGAD	Refractory to (relapse* breakthrough) at least two treatments; one must be prednisolone and an immunosuppressant (any of mycophenolate mofetil/rituximab/azathioprine/methotrexate) **OR** Serious side effects with prednisolone (adequate dose and length of time)	Pseudo-relapse **OR** MS (may have low positive MOGAbs)	Failed 2 first line therapies	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes
AQP4 NMOSD	Failed or intolerant to 3 or more 'usual treatments' resulting in relapse*, including at least prednisolone (unless severe prednisolone side effects from adequate dose and time) and immunosuppressant(azathioprine/rituximab/mycophenolate mofetil/methotrexate/ciclosporin or tacrolimus/plasma exchange or new randomised controlled trial treatment if available)	Pseudo-relapse	As per selection criteria	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes
Ab negative phenotypes	Failed or intolerant to 3 or more 'usual treatments' resulting in relapse* including at least prednisolone (unless severe prednisolone side effects from	Pseudo-relapse **OR** other inflammatory disease diagnoses (e.g.	As per selection criteria	1 g/kg daily over 2 days then 1 g/kg monthly for first year (titrate to 2 g/kg if relapses occur despite steroids and	Suppression of further relapses* Treatment failure – defined as objective evidence of true relapse* on treatment	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
	adequate dose and time) and immunosuppressant (azathioprine/rituximab/mycophenolate mofetil/methotrexate/ciclosporin or tacrolimus/plasma exchange or new randomised controlled trial treatment if available	MS Sarcoid, Behcets etc)		standard 1 g/kg monthly dosing) Annual assessments required for dose optimisation and ongoing therapy		

*Attack or relapse is a new or extended neurological symptom with signs that reflect the anatomical location of the inflammatory lesion (note a minority of MOGAD TM may be difficult to visualise) that is not a fluctuating residual symptom of an old lesion and that usually persists for at least one week. However, acute treatment should not be delayed. Contrast enhancement is present in the majority during the acute phase.

Opsoclonus-myoclonus syndrome (OMS)- paediatric or adult non-paraneoplastic	• Paediatric OMS diagnosed by a paediatric neurologist **OR** • OMS in an adult with no evidence of neoplasm, anti-neuronal antibodies, or focal structural or inflammatory alternative diagnosis	Structural disease. Multiple sclerosis or other inflammatory lesions associated with defined diagnoses where the primary treatment of that disease is not Ig	Corticosteroids should be tried first Consider other anti-inflammatory strategies including oral immunosuppressants, rituximab or cyclophosphamide as appropriate	2 g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability	Improvement in OMS score	Yes
Paraneoplastic neurological syndromes (PNS) without evidence of autoantibodies	• Defined paraneoplastic syndrome (for example limbic encephalitis, sensory ganglionopathy, cerebellar degeneration etc) **AND** • Evidence of a PNS associated tumour (e.g. small cell lung, ovarian or testicular, breast, thymoma etc)	See eligibility criteria	Treatment of primary tumour Consider steroids and plasma exchange	2 g/kg over 5 days initially repeated at 6 weeks. If beneficial then titrated to optimal interval and minimum dose to achieve stability. Discontinue If not objectively effective after 2 doses.	Clinically meaningful improvement in • Modified Rankin Scale • 10m walk • Any validated relevant disability measure appropriate to the condition	Yes
Rasmussen's Encephalitis	• When other therapies (such as steroids) have failed	No specific exclusion criteria but see General notes regarding pro-thrombotic risks of Ig	Ig is reserved for patients unresponsive to steroids and other therapies.	2g/kg given over 2 -- 5 days and repeated monthly for three months for initial trial	Seizure frequency with expected reduction of 30% to continue therapy	Yes

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Stiff person syndrome (SPS) or variant	Diagnosis of SPS or a variant (stiff limb, progressive encephalomyelitis with rigidity and myoclonus [PERM], etc) by a consultant neurologist Supportive criteria: • Demonstration of auto-antibodies to GAD, DPPX, amphyphysin, gephyrin or other stiff person associated antibodies **AND/OR** • Continuous motor unit activity at rest on EMG testing in paraspinal or affected limb musculature	No specific exclusion criteria but see General notes regarding pro-thrombotic risks of Ig	Consider plasma exchange as initial treatment Rituximab is likely to be equally effective but is not commissioned for this indication	An initiation regimen of a maximum 4 g/kg divided into at least two courses of 1 – 2 g/kg each and given over a 4 - 8 week period, with assessment at the end of the period. Regimens to establish response might include: • 2 g/kg given over 2 - 5 days and repeated after 6 weeks.[22]. • 2 g/kg initially followed by 1 g/kg after 3 weeks and a further 1 g/kg 3 weeks later[213] For maintenance dose optimisation see general note below. If no significant measurable and functionally meaningful improvement in abilities has been achieved after 3 doses Ig should be stopped.	Clinically meaningful improvement in at least two of the measures below: • Stiffness • Up and go 10-m walk (in secs) • BRIT score • Number of spasms per day • Validation measure of functional abilities	Yes

For many disorders where rituximab is a potential longer-term alternative to IVIg, the speed of response should be considered in determining treatment choice.
IVIg can provide more rapid but temporary control and is likely to be the preferred option in emergency situations where an immediate response is required, for example in dysphagia and/or difficulty in breathing in inflammatory myositis.

Use of Immunoglobulin in Infectious Diseases

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Hepatitis A	Ig is recommended in addition to hepatitis A vaccine for contacts of hepatitis A who are less able to respond to vaccine • those aged 60 or over, **OR** • those with immunosuppression and those with a CD4 count <200 cell per microlitre, **OR** • those at risk of severe complications (those with chronic liver disease including chronic hepatitis B or C infection)	See eligibility criteria	Hepatitis A vaccine is recommended in addition to Ig Vaccine should be administered within 2 weeks of exposure	Subgam: <10 years 500mg >10 years 1000mg To be given by intramuscular injection *(*Please note SPC currently indicates subcutaneous route of administration only [although previously indicated both s/c and im routes], UKHSA guidance recommends intramuscular administration for post-exposure prophylaxis with Subgam) Given with vaccine in those at high risk, within 2 weeks of exposure (those over 60 years, immunosuppression, CD4 count <200 cell per microliter) and those at risk of severe complications. For those exposed between 2 - 4 weeks ago, Ig may also be offered to modify disease in those at risk of severe complications (i.e. chronic liver disease including chronic hepatitis B or C infection).	Outcome measures not routinely recorded on surveillance databases Ig is issued nationally and locally; records are held of who Ig was issued for with respect to exposure to the hepatitis A virus.	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Measles (immunosuppressed individuals)	Immunosuppressed individuals (Group A and Group B based on level of immunosuppression[29]) who have had a significant exposure to measles and are known to be susceptible (based on vaccine history and/or IgG testing).	See eligibility criteria	For immunosuppressed contacts Ig is the mainstay of management	0.15 g/kg of IVIg recommended ideally within 72 hours of exposure although can be given up to 6 days. Where exposure recognised late or found to be antibody negative between 6 and 18 days after exposure, IVIg may be considered following discussion with specialist clinician.	Prevention of measles	Prior approval is via discussion with UKHSA health protection team *Find your local protection team here: https://www.gov.uk/health-protection-team

[29] UK Health Security Agency. National measles guidelines. Available from: *National measles guidelines July 2024*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
Measles (pregnant women and infants)	Pregnant women who have identified as susceptible based on vaccine history and /or antibody testing who have had a significant exposure to measles. Infants under 9 months of age with a significant exposure to measles. Advice is available at: National measles guidelines - GOV.UK	See eligibility criteria	For pregnant contacts, Ig is mainstay management for post-exposure prophylaxis For infants below 6 months Ig is mainstay treatment; For infants aged between 6 - 8 months, MMR vaccine can be offered if exposure occurred outside household setting AND ideally should be given within 72 hours	• For pregnant contacts, approximately 3000mg of human normal Ig (HNIG) • Infants 0.6 ml/kg up to a maximum of 1000mg of HNIG HNIG to be given within 6 days of exposure in pregnant women and infants. The National Measles Guidance (referenced in column 2), Section 2.3.2 recommends these doses are administered IM, using the SC formulations, as long as use via this route is acknowledged to be off-label.	Prevention of measles	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Polio	To prevent or attenuate an attack: • An immunocompromised person inadvertently given live polio vaccine, **OR** • An immunocompromised person whose contacts are inadvertently given live polio vaccine	See eligibility criteria	Ig represents 1st line treatment	<1 year: 250mg 1 – 2 years: 500mg >3 years: 750mg Stool samples from the immunosuppressed individual must be obtained one week apart. If poliovirus is grown from either sample, repeat Ig at 3 weeks. Continue weekly stool collection and administration of Ig 3- weekly until immunocompromised individual's stool is negative for poliovirus on two occasions	Prevention or resolution of infection	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Severe or recurrent Clostridium difficile infection (CDI) colitis - short term use	• Severe cases (WCC >15 and/or acutely rising creatinine and/or signs/symptoms of colitis) not responding to routine 1st line vancomycin and metronidazole • If multiple recurrences, especially with evidence of malnutrition	See comments under position of Ig	For fulminant or recurrent CDI unresponsive to appropriate antibiotics (see under selection criteria) consider IV tigecycline or Ig[30]. Faecal microbiota transplantation is approved by NICE for patients with recurrent CDI unresponsive to antibiotics and is likely	0.4 g/kg, one dose, and consider repeating once	• Clearance of C. diff. • Duration of hospital in-patient stay	Yes

[30] McDonald et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Clin Infect Dis 2018;66:e1-e48

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			to be an effective alternative[31].			
Staphylococcal (including PVL-associated sepsis) or streptococcal toxic shock syndrome (TSS) - short term use	• Diagnosis of streptococcal or staphylococcal TSS, preferably with isolation of organism, **AND** • Failure to achieve rapid improvement with antibiotic therapy and other supportive measures, **AND** • Life-threatening	See comments under position of Ig	Ig is reserved for patients with life-threatening disease who fail to achieve rapid improvement with antibiotic therapy. However, for **streptococcal TSS**, it should be noted that there has been significant controversy regarding the benefits of Ig treatment prompting the Infectious Diseases Society of America (IDSA) not to recommend its use in patients with necrotising Group A streptococcal infections.[32] Since then a systematic review and meta-analysis of Ig in clindamycin-treated patients with streptococcal TSS suggests a reduction in mortality from 33.7% to 15.7%, though this finding may be confounded by differences in baseline characteristics between patients receiving IVIg and those who did not.[33] Based on the results of this meta-analysis, the use of IVIg as adjunctive therapy is	Total dose of 2 g/kg, because of uncertainty regarding the timing and optimal dose of Ig, it is recommended that patients are reviewed after an initial dose of 1 g/kg. Should there be no evidence of improvement at 24 hours, a further 1 g/kg may be considered.	• Improvement of FBC, ALK, CPK and acute phase markers • Reduction in hospital inpatient stay • Survival	Yes If prior approval is not possible, then treatment should proceed, and retrospective approval should be sought.

[31] National Institute for Health and Care Excellence. Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]. Available from: *Overview | Faecal microbiota transplant for recurrent Clostridium difficile infection | Guidance | NICE*

[32] Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. 2014 update by the IDSA. Clin Infect Dis 2014;59:e10-52

[33] Parks T et al. Clin Infect Disease 2018;67:1434-6

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			supported by Stevens DL.[34]			
Suspected tetanus case	Person with clinical symptoms suggestive of localised or generalised tetanus ("in the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia AND diagnosis of tetanus by a healthcare provider") Guidance on the management of suspected tetanus cases and the assessment and management of tetanus-prone wounds - GOV.UK	See eligibility criteria	• Wound debridement • Antimicrobials • Ig based on weight • Supportive care • Vaccination with tetanus toxoid following recovery	**Ig – intravenous (IVIg):** Dosage based on equivalent dose of anti-tetanus antibodies of 5000 IU for individuals < 50kg and 10000 IU for individuals > 50kg	Resolution of tetanus infection	No
Tetanus prone injury (prophylaxis)	Tetanus specific Ig (TIg) has limited stock and is recommended for susceptible individuals sustaining high risk tetanus prone injuries as defined in guidance.[35]	See eligibility criteria	• Thorough cleaning of wound essential • Ig for Prophylaxis • Booster of tetanus-containing vaccine for long term protection	**Tetanus specific Ig – intramuscular (IM-TIg)** • 250 IU for most uses • 500 IU if more than 24 hours have elapsed or there is a risk of heavy contamination or following burns The dose is the same for adults and children **Ig – subcutaneous (SCIg) / intramuscular (IMIg):** If TIg (for im use) cannot be sourced, Ig for subcutaneous or intra-muscular use may be given as an alternative. Based on testing for the presence of anti-tetanus antibodies of alternative Ig products, the volume required to achieve the recommended dose of 250 IU are included: Guidance on the management of suspected tetanus cases and the assessment and management of tetanus-prone wounds - GOV.UK. Although no time frame is specified in the guidance, IM-TIg/Ig following a tetanus prone wound is only likely to confer	Prevention of tetanus infection	No

[34] UpToDate. Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention. Available from: *Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention - UpToDate*

[35] Public Health England. Tetanus: advice for health professionals. Available from: *Tetanus information for health professionals (publishing.service.gov.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
				benefit when given within incubation period of tetanus (10-21 days)		
Varicella zoster	Individuals for whom oral antivirals are contraindicated due to malabsorption or some cases of renal toxicity. Ig is indicated for those individuals who fulfil all of the following: 1) Significant exposure to chickenpox (varicella) or shingles (zoster) during the infectious period 2) At increased risk of severe chickenpox i.e. immunosuppressed individuals, neonates and pregnant women 3) No antibodies to varicella-zoster virus (based on VZV antibody testing) 4) Unable to take oral antivirals due to malabsorption or renal toxicity Updated guidance on post exposure prophylaxis have been published in January 2025. Advice is available at: https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles Neonates of mothers who have developed chicken pox within 7 days of birth (either before or after delivery and who cannot obtain Varitect (Varicella-zoster immunoglobulin) in a timely manner.	Unless contra-indicated, oral antivirals would be considered first-line Neonates treated with Varitect	Oral antivirals are considered first-line	0.2 g/kg (i.e. 4 ml/kg for a 5 % solution) Brands have not been specified as no formal testing of products has been undertaken IVIg should be administered ideally within 7 days of exposure in eligible individuals. Where the exposure has been identified beyond 7 days, IVIg can be offered up to 14 days after exposure.	• Prevention of chicken pox infection • Prevention of severe chicken pox • Prevention of chicken pox infection • Prevention of severe chicken pox	Prior approval is via discussion with UKHSA health protection team Find your local protection team here: https://www.gov.uk/health-protection-team
Viral pneumonitis post-transplantation: HSCT and solid organ	Definitive diagnosis of viral pneumonitis – Varicella Zoster Virus (VZV), Respiratory Syncytial Virus (RSV), Human Parainfluenza Virus (HPIV)	**VZV** - See comments under position of Ig **RSV/HPIV** – patients with mild disease confined to the upper respiratory tract	**VZV** – Ig is reserved for patients with disseminated disease. For guidance on treatment of patients with significant exposure to chickenpox or herpes zoster please see use of Ig in specific infectious diseases.	1 – 2 g/kg in divided doses	• Radiological improvement • Length of hospital stay • Survival	Yes If prior approval is not possible then treatment should proceed, and retrospective approval should be sought.

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database)	Prior panel approval required
			RSV, HPIV – patients with lower respiratory infections. In patients with RSV infection, Ig would be used as an adjunct to ribavirin. **RSV, HPIV** - **patients with RSV and HPIV upper respiratory infections post-HSCT**. Consider Ig in the presence of some or all of the following risk factors.[36] • Older age • Graft-versus- host disease • Lymphopenia: <0.2 x 10^9/L • Neutropenia • Mismatched/unrelated donor • Immediate aftermath of HSCT (<1 month)			

[36] Hirsch et al. Clin Infect Dis. 2013 Jan 15; 56(2): 258–266

Use of Immunoglobulin in "Other" Indications

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
Allo-immune neonatal haemochromatosis or gestational allo-immune liver disease (GALD)	• Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of foetal haemochromatosis **OR** • Women who have had an offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis • Affected neonates • Decision to treat with Ig made by a consultant obstetrician with input from a liver unit specialist	None	For those patients fulfilling eligibility criteria, there are no alternatives to Ig For further information please refer to the NHS England Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis[37]	Maternal dose: Ig is administered by intravenous infusion at a dose of 1 g/kg (dose capped at 60 g per week) to at risk mothers at 14 weeks, 16 weeks and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks. The weight used to calculate the dose will be the mother's weight at booking. Neonatal dose: 1 g/kg The need for repeated doses, which may be required in exceptional cases, should be based on clinical need and locally agreed policy.	• Foetal loss (including gestation) • Gestation at delivery • Neonatal outcomes	Yes .
ANCA-associated systemic vasculitides (AAV)	• Patients with refractory/relapsing AAV in whom conventional immunosuppressive therapy is contra-indicated e.g. presence of severe infection or in pregnancy as bridging therapy • The role of Ig in the treatment of ANCA-negative small vessel vasculitis is unclear, and each case will need to be assessed on individual grounds.	No specific exclusion criteria – see comments under selection criteria	Ig is reserved as adjunctive or very rarely as sole therapy for the minority of patients in whom conventional immunosuppressive therapy is contra-indicated	Total dose of 2 g/kg over 2 – 5 days every 4 weeks. The optimal duration of therapy is not known though most patients are likely to achieve remission after 3 months. Ig should be discontinued after 3 months in the absence of clinical improvement.	• Clinically meaningful improvement in Birmingham Vasculitis Score (BVAS)/PVAS - to capture paediatric assessment tool • Fall in inflammatory markers • Improvement in organ function	Yes
Autoimmune uveitis - short term use	• Severe aggressive sight-threatening disease unresponsive to conventional immunosuppressive treatment (topical and systemic steroids and oral or injectable immunosuppressants)	See comments under position of Ig	Ig is reserved for exceptional cases where conventional immunosuppressive agents are contra-indicated or ineffective or associated with intolerable adverse effects, especially in the context of autoimmune retinopathy. Adalimumab is regarded as the treatment of choice for other forms of severe, refractory uveitis and is	1 - 1.5 g/kg 2 – 3 infusions given 6 – 8 weeks apart to assess benefit	• Clinically meaningful improvement or stabilisation in visual acuity • Imaging endpoints • Electrodiagnostic studies	Yes

[37] National Health Service. Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of alloimmune fetal and neonatal haemochromatosis. Available from: *1864_Maternal-intravenous-immunoglobulin-to-prevent-allo-immune-fetal-haemochromatosis.pdf (england.nhs.uk)*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
			routinely commissioned by NHS England. (NICE TA460[38]). Infliximab is not routinely commissioned by NHS England for this indication.[39]			
Catastrophic antiphospolipid syndrome (CAPS)	Diagnosis of definite or probable CAPS: • Thromboses in 3 or more organs developing in less than a week • Histological evidence of microthrombosis in at least one organ • Persistent anti-phospholipid antibody positivity (lupus anti-coagulant and or anti-cardiolipin/anti-B2GPI of IgG or IgM isotype	Chronic recurrent thrombosis due to other causes Thrombosis associated with stable anti-phospholipid syndrome in the context of other disorders	Steroids, anticoagulants and plasma exchange) represents optimal therapy Ig is likely to be beneficial in selected cases associated with severe thrombocytopenia where plasma exchange is either unavailable or contra-indicated or in the event of deterioration following plasma exchange	2 g/kg over 4 - 5 days	• Clinically meaningful improvement • Reduction in anti-phospholipid antibody levels	Yes
Immunobullous diseases - long term use	• Severely affected **AND** • Conventional corticosteroid treatment with adjuvant immunosuppressive agents has failed or is inappropriate	See comments under position of Ig	Ig is reserved as adjunctive therapy for patients with severe disease refractory to conventional immunosuppressive therapy. Rituximab is increasingly supplanting Ig as the preferred treatment for resistant disease and is routinely commissioned by NHS England[40] .In such patients it is listed as a 3rd line treatment alongside Ig. However, rituximab should be favoured over Ig, given the stronger evidence base supporting its use.	1 - 2 g/kg over 2 – 5 days. There may be a need for maintenance Ig in exceptional patients unresponsive or intolerant of rituximab. In such cases every attempt should be made to define the minimal effective dose of Ig by undertaking periodic dose reduction and or lengthening the interval between treatment	• Reduction in recurrence of disease/relapse • Dose reduction/discontinuation of other immunosuppressive therapy • Improved quality of life • Resolution of blisters/healing affected skin • Resolution of pruritus	Yes
Kawasaki disease – short term use	Clinical diagnosis of Kawasaki disease by a paediatrician, paediatric infectious disease	None	Ig in combination with anti-inflammatory doses of aspirin is the treatment of choice	2 g/kg single dose, in conjunction with high-dose aspirin; a second dose may be	• Resolution of fever • Improvement in acute phase markers	No

[38]National Institute for Health and Care Excellence: *Adalimumab and dexamethasone for treating non-infectious uveitis.* Available from*:* *Overview | Adalimumab and dexamethasone for treating non-infectious uveitis | Guidance | NICE*

[39] National Health Service. Clinical Commissioning Policy: Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis. Available from: *d12pb-paediatric-pats-uveitis-inflixi-fin.pdf (england.nhs.uk)*

[40] National Health Service. Clinical Commissioning Policy: Rituximab for Immunobullous Disease. Available from: *https://www.england.nhs.uk/wp-content/uploads/2021/06/cc-policy-rituximab-for-immonobullous-disease-ocular-v2.pdf*

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
	consultant or paediatric immunologist			given if no response, or if relapse within 48 hrs		
Paediatric inflammatory multisystem syndrome temporarily associated to COVID-19 (PIMS-TS) - short term use	Clinical diagnosis of PIMS-TS by a paediatrician, paediatric consultant in infection or paediatric immunologist Clinical diagnosis of PIMS-TS in an adult (also known as MIS-C or AIMS-TS) by a consultant in infection or immunologist or appropriate specialist MDT Because of the similarities between PIMS-TS and Kawasaki disease, the use of Ig was approved in 2020 for any child fulfilling diagnostic criteria for PIMS https://www.rcpch.ac.uk/. More recent data suggests that steroids should be considered as first-line therapy, especially for children 6 years old and over without symptoms of Kawasaki disease – see comments under position of immunoglobulin.		Consider steroids as first-line therapy while reserving IVIg for those cases where there is difficulty in distinguishing Kawasaki disease from MIS-C. In practice, this is particularly challenging in children under 6 years in whom IVIg may need to be considered as first-line therapy. IVIg was originally recommended as a first-line treatment for MIS-C based on its clinical similarities to Kawasaki disease. New data from an international observational cohort of 2009 patients with MIS-C from 39 countries randomised to receive IVIg alone (n=680), IVIg plus steroids (n= 698) and steroids alone (n=487) suggests that initial treatment with steroids was a safe and effective alternative to IVIg or combined therapy.[41] There were no significant differences between treatment arms for primary outcomes – need for ventilation, inotropic support or death. In addition, the occurrence and resolution of coronary artery aneurysms did not differ significantly between treatment groups.		

[41] Channon-Wells et al Lancet Rheumatology 2023;5:e184-99

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
Prevention of autoimmune congenital heart block (CHB) (anti-Ro)	**Prophylactic** Ig therapy has previously been given during pregnancy when: • There is a history of autoimmune congenital heart block in at least one previous pregnancy, **AND** • Maternal anti-Ro and/or anti-La antibodies are present. However, more recent evidence has cast doubt on the beneficial effects of Ig with hydroxychloroquine being regarded as 1st line therapy – see comments under position of immunoglobulin	See comments under position of Ig	Hydroxychloroquine is regarded as the treatment of choice. Ig may be considered in exceptional cases refractory to hydroxychloroquine or if the patient is unable to tolerate hydroxychloroquine, but there is uncertainty regarding its efficacy. At a dose of 0.4 g/kg every 3 weeks administered from weeks 12 through to week 24 of gestation, immunoglobulin was ineffective in preventing the development of CHB in neonates in two prospective open-label trials; based on a case series a higher dose (1 g/kg) alongside high dose oral prednisolone may possibly be effective.	Two infusions of 1 g/kg/day, the first at 14 weeks and the second at 18 weeks of gestation The weight used to calculate the dose will be the mother's weight at booking.	Improvement in the degree of heart block at birth	Yes
Transplantation (solid organ) – short term use	**Antibody Incompatible Transplant (AIT)** Patients in whom renal, heart, liver or lung transplant is prevented because of antibodies **Antibody Mediated Rejection (AMR)** Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart, liver and/or lung transplant	See comments under position of Ig	While Ig is included in many protocols, there is a paucity of high-quality evidence to support its use. A systematic review of AMR in kidney transplant recipients categorised the evidence supporting the use of IVIg as being 'very low.'[42] Where Ig is used in combination with plasma exchange, any beneficial effects of Ig are likely to be negated by subsequent plasma exchange. For this reason, the use of Ig immediately prior to plasma exchange is not supported. The addition of rituximab to Ig appears to	**AIT:** Up to 2 g/kg to be repeated as per Donor Specific Antibodies (DSA); in renal desensitisation at 0.1 g/kg for 8 – 12 doses **AMR:** Treatment protocols vary in the UK ranging from low dose 100mg/kg after plasma exchange or high dose 2g/kg	**AIT and AMR:** Renal: • Type of renal transplant • HLA class DSA (where available) • Rejection episodes • Patient survival • Graft survival • Renal function = eGFR (MDRD) • Cardiothoracic: • DSA • Length of ITU and hospital stay • Graft function (heart = rejection fraction; lung = spirometry; liver = liver function, clotting indices)	No

[42] Roberts DM et al. The treatment of acute antibody-mediated rejection in kidney transplant recipients – a systematic review. Transplantation. 2012;94:775-783

Indications	Eligibility criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Outcome measures (to be recorded on the national immunoglobulin database	Prior panel approval required
			be of benefit in lowering HLA antibody titres			
Scleromyxedema	Patients will be eligible for Ig treatment if they fulfil **ALL** of the following criteria: • Diagnosed with scleromyxedema following a biopsy by a joint rheumatology and dermatology clinic within a rheumatology or dermatology specialised centre with expertise in autoimmune connective tissue disease. • The diagnosis was made in line with the widely acknowledged scleromyxedema diagnostic classification (Rongioletti and Rebora, 2001) where the patient should have ANY three of the following four criteria: o Generalised, papular and sclerodermoid eruption o Presence of monoclonal gammopathy o Absence of thyroid disease o Histological triad of mucin deposition, fibroblast proliferation and fibrosis as confirmed by biopsy	Patients with contraindications to therapy with human normal immunoglobulin are not eligible for treatment.	First, second or any line treatment. Clonal plasma cell is a key feature of scleromyxoederma. Consider plasma cell-directed therapies (anti-CD38, proteosome inhibitors, lenalidomie and its analogues) as an alternative to Ig.	Starting dose is 1-2g/kg by ideal body weight initially delivered at a frequency of every 4 weeks. Initially treatment should be delivered over 2-5 days. The dose can be modified according to treatment response Please refer to NHS England policy Human normal immunoglobulin for scleromyxedema (adults) Dose adjustment: Dose adjustment should be considered at 3, 6 and 12 months after starting treatment. The dose can be reduced by increasing the interval between treatments up to 6 weekly rather than 4 weekly. Alternatively, the dose given during each infusion can be reduced from 2g/kg. The minimum effective clinical dose to maintain remission should be established for each individual patient.	At 3, 6 and 12 months after starting treatment and beyond: • Absence or presence of systemic involvement, including progression to dermatoneuro syndrome as a marker of neurological involvement • Hospital admissions per year relating to scleromyxedema • Modified Rodnan skin score • Level of paraprotein	Yes

General notes: Dosing optimisation in neurology for maintenance

An ongoing issue for diseases that require long-term Ig treatment is that once significant and functional responsiveness to intravenous Ig (IVIg) is demonstrated for a patient using standard immunomodulatory dosing, the 'maintenance' dosing required to maintain the therapeutic response is not well characterised. In this update, the dosing recommendations for some neurological indications include 'time to relapse' as the interval between doses. This approach is supported by evidence from The Oxford Programme for Immunomodulatory Immunoglobulin Therapy, which was set up to review multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treatment with immunoglobulin. In view of the uncertainty of both remission and disease progression in CIDP and MMN, The Oxford Programme reviewed the dose and infusion frequency of patients on a regular basis and showed that increasing the infusion interval proved successful in some patients and resulted in treatment discontinuation[43]. Very rarely, a small minority of patients with CIDP and MMN may require higher doses of Ig (> 2g/kg/every 6 weeks) as maintenance treatment. Such patients should be closely monitored either in or in close liaison with specialist centres with specific expertise in the management of autoimmune neuropathies. Regular reasonable disease-relevant attempts should be made to establish continued requirements or the minimum effective dose by supported cessation trials, down titration of dose or extending the interval between infusions.

An alternative approach based on establishing the 'time to relapse' following the first or second dose followed by dose reduction has also been proposed and is equally feasible20. This ensures patients who need no more than 1 or 2 doses are not exposed to unnecessary doses and those with ongoing needs are optimised to a minimal dose.

Based on evidence from randomised trials, it is likely that up to 40% of patients with CIDP may be able to discontinue treatment[44] after 6 - 12 months, although a significant proportion may relapse and require retreatment. For this reason, periodic trials of cessation of treatment are recommended, especially in patients who appear to be stable even if optimally treated. The demonstration of continued IVIg requirement by forced suspension on more than 2 or 3 occasions over a 5-year period probably indicates ongoing long-term dependence and further withdrawals are highly unlikely to be effective. Referral to a specialist neurology centre is recommended as early as possible.

In inflammatory myositis, maintenance treatment with IVIg for a prolonged period (usually less than 12 months) may be required in a small minority of patients. In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be attempted at least annually to establish on-going need for treatment[45].

[43] Lucas M et al. J Clin Immunol. 2010 May;30 Suppl 1:S84-9.
[44] Adrichem M et al. J Peripher Nerv Syst. 2016 Sep;21(3):121-7.
[45] Foreman et al. Internal Med J 2017;47:112-115

For those disease indications in children and young adults where IVIg and plasma exchange (PLEX) are equally efficacious, IVIg may be preferentially considered if poor peripheral venous access or challenges in service delivery preclude the use of PLEX.

Specific exclusion criteria against the use of immunoglobulin have not been listed, but it is important to carry out benefit-risk analyses in certain patient groups: patients at high risk of thromboembolism (hypertension, diabetes, smoking, hypercoagulable states) should be counselled regarding the prothrombotic risks of immunoglobulin.

IgA deficiency is no longer considered a contra-indication to the use of immunoglobulin and should not be withheld because of theoretical concerns of adverse reactions. The role of anti-IgA antibodies in causing reactions is controversial and measurement of anti-IgA antibodies prior to undertaking treatment is not warranted.

Appendix B – Not Routinely Commissioned Indications

The Ig Expert Working Group (EWG) concluded that there was either insufficient evidence to support the routine commissioning of Ig to treat the following indications or that there was evidence to support a not routinely commissioned position:

- Acquired red cell aplasia NOT due to parvovirus B19
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Aplastic anaemia NOT due to parvovirus infection
- Asthma
- Atopic dermatitis/eczema
- Autoimmune neutropenia
- Autologous BMT
- Cerebral infarction with antiphospholipid antibodies
- Chronic facial pain
- Chronic fatigue syndrome
- Chronic idiopathic urticaria
- Chronic immune thrombocytopenia (ITP)
- Chronic regional pain syndrome
- CNS vasculitis
- Critical illness neuropathy
- Diabetic neuropathy
- Graves' ophthalmopathy
- Haemolytic uraemic syndrome
- Immunodeficiency secondary to paediatric HIV infection
- Inclusion body myositis
- Intractable childhood epilepsy
- IVF failure
- Multiple sclerosis
- Neonatal sepsis (prevention or treatment)
- Opsoclonus-myoclonus syndrome - adult carcinoma related
- Paediatric myocarditis
- PANS/PANDAS
- Paraneoplastic syndromes not known to be T or B cell mediated
- POEMS (polyneuropathy organomegaly, endocrinopathy/oedema, monoclonal protein, skin changes)
- Pyoderma gangrenosum
- Recurrent spontaneous pregnancy loss
- Rheumatoid arthritis
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- SLE with secondary immunocytopenias
- Systemic juvenile idiopathic arthritis
- Toxic epidermal necrolysis, including Steven Johnson Syndrome

Single Technology Appraisal

Talquetamab for treating relapsed or refractory multiple myeloma after 3 treatments [ID5082]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 9 June 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Major Issues (Ordered by Importance)

Issue 1 Additional critical details required in EAG critique of overall survival (OS) indirect treatment comparison (ITC) hazard ratio (HR)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 1A: EAG critique of OS ITC HR			
Page 19, Executive Summary The EAG raised concerns regarding the reliability of the ITC HR for OS, noting the following: "These are based on the following: a] The ITC appears not to have considered the impact of COVID 19 upon the survival of the unvaccinated MajesTEC-1 population. This would result in an underestimate of teclistamab survival and a HR more favourable to talquetamab than warranted.	Remove any discussion of regression analysis studies and how their results may impact the interpretation of the OS and PFS ITC HRs, given the major limitations associated with both studies which invalidate their application to the talquetamab versus teclistamab ITC HRs Additionally, the limitations associated with the real-world evidence studies, and therefore any conclusions that can be drawn from them, should be correctly described. Please amend the text as follows (suggested additions marked in bold, suggested removals marked as a strikethrough): Page 19, Executive Summary	The reasons provided by the EAG related to concerns with the reliability of the ITC HR for OS for talquetamab versus teclistamab are associated with the following limitations : The results of the regression analyses studies are not applicable to the OS HR reported in the CS • A white paper on surrogate endpoints was jointly published by the National Institute for Health and care Excellence (NICE), the Canadian Drugs Agency (CDA), the Institute for Clinical and Economic Review (ICER) and.[1] As outlined in the paper, for transferability of surrogacy to other contexts based on validation studies, **population, interventions and mechanism of action,** setting in which data are collected (e.g., RCTs) as well as **disease and disease stages** need to be aligned.[1] • The studies included in the regression analysis studies provided within in the EAG report however are not aligned with the trial	Comments made are points of disagreement not factual errors. The only changes to the EAG report are detailed below • **Page 19** a] The ITC appears not to have considered the impact of COVID 19 upon the survival of the unvaccinated MajesTEC-1 population. This **could** ~~would~~ result in an

b] Regression studies of phase 3 studies indicate that the company's ITC HR of [redacted] (based on two different single arm studies) is an outlier and is over favourable to talquetamab. c] Recently published real-world studies from Europe suggest that the company's ITC dependent modelling of talquetamab survival is over optimistic while the modelling of teclistamab is over pessimistic. This suggests there will be bias that favours talquetamab over teclistamab in the company's economic analysis" Page 107, Section 3.4.5 The EAG commented the following: "There is uncertainty regarding the ITC OS HR that is applied to the teclistamab calibrated lognormal model. This rests of	"These are based on the following: a] The ITC appears not to have considered the impact of COVID 19 upon the survival of the unvaccinated MajesTEC-1 population. This **could** ~~would~~ result in an underestimate of teclistamab survival and a HR more favourable to talquetamab than warranted. ~~b] Regression studies of phase 3 studies indicate that the company's ITC HR of [redacted] (based on two different single arm studies) is an outlier and is over favourable to talquetamab.~~ c] Recently published real-world studies from Europe **are inconclusive in suggesting whether the results of MonumenTAL-1 versus MajesTEC-1 may overestimate effectiveness of talquetamab**~~suggest that the company's ITC dependent modelling of talquetamab survival is over optimistic while the modelling of teclistamab is over pessimistic~~"	data considered in the CS in terms of population or disease stage (i.e., none of the included studies are TCE RRMM specific). Furthermore, neither study includes any evidence on bispecific antibodies, meaning that they have extremely limited relevance to the comparison between talquetamab and teclistamab that underpins this NICE submission. Indeed, a clear caveat was mentioned by Etekal *et al.* cautioning the applicability of the regression analyses to BsAbs, stating the following: **"As no randomised trials have yet [been] reported for other agents such as bispecific agents and chimeric antigen receptor therapy, our results may not be applicable to those settings**."[2] • As such, these regression analysis studies do not fulfil the requirements for surrogacy analysis outlined in the NICE white paper (Nov 2024). The relevance of the relationship between OS and PFS HRs outlined within these studies to the HRs reported within the CS is therefore unfounded.[1-3] As such, any analysis and associated conclusions based on these regression studies are flawed and should be removed from the EAG report to avoid introducing substantial uncertainty. • Full details on the lack of transferability of the results of the regression studies to the	underestimate of teclistamab survival and a HR more favourable to talquetamab than warranted.

several considerations: a] the patients in MajesTEC-1 were recruited during the COVID 19 pandemic and were not vaccinated against the virus; the teclistamab model to which the HR is applied appears to be unadjusted for the mortality that may be attributable to COVID-19 and therefore may underestimate the true survival of teclistamab recipients; b] published regression analyses of phase 3 studies indicate the company's HR based on two single arm studies may be an outlier. c] recently publishes real world studies are consistent with the company's likely over-estimation of survival of talquetamab recipients and underestimation of survival of teclistamab recipients" Page 187, Section 5.6	Page 107, Section 3.4.5 "There is uncertainty regarding the ITC OS HR that is applied to the teclistamab calibrated lognormal model. This rests **on**~~of~~ several considerations: a] the patients in MajesTEC-1 were recruited during the COVID 19 pandemic and were not vaccinated against the virus; the teclistamab model to which the HR is applied appears to be unadjusted for the mortality that may be attributable to COVID-19 and therefore may underestimate the true survival of teclistamab recipients~~; b] published regression analyses of phase 3 studies indicate the company's HR based on two single arm studies may be an outlier. c~~**b**] recently **published**~~publishes~~ real world studies are **inconclusive in suggesting whether the results of MonumenTAL-1 versus MajesTEC-1 may overestimate the effectiveness of talquetamab** ~~consistent with the company's likely over-estimation of survival of talquetamab recipients and~~	ITC HRs reported in the CS are presented in Issue 1B below. <u>Inaccurate reporting of outcomes from real-world studies and lack of generalisability of non-UK real-world studies to UK clinical practice</u> • The EAG's conclusions about European real-world studies are factually inaccurate. The EAG have presented incorrect OS data from the Perrot et al. study; the correct OS data shows that survival is worsened in the Perrot et al. study compared to MajesTEC-1. The EAG's conclusions regarding these real-world evidence (RWE) studies are therefore fundamentally flawed and should be removed from the EAG report. • Moreover, the inclusion of non-UK real-world studies does not resolve the EAG's concerns regarding the generalisability of data to UK clinical practice where the non-UK RWE are fundamentally different from UK clinical practice, with no further adjustments applied. • Full details of the limitations associated with the presented real-world evidence are presented in Issue 1C below. Whilst J&J IM acknowledge that there may be inherent uncertainty associated with ITC analyses, the current discussion of the resulting HRs in the EAG report creates a misleading and inaccurate impression of the relative strengths of the data and the methodologies employed. The current	• **Page 107** This rests **on**~~of~~ <u>Inaccurate reporting</u> We thank the J&J IM for pointing out the error in the Perrot plot. The EAG has corrected plot errors and modified inferences accordingly. **EAG entire updated 3.4.7.2 Section.**

"The EAG found that the company's ITC methods are likely to have resulted in potential biases in favour of talquetamab, which transcends to the company's economic model. The key concerns around the company's ITC are: • The ITC does not appear to consider the impact of COVID-19 upon the survival of the unvaccinated MajesTEC-1 population. This would result in an underestimate of teclistamab survival. • Regression studies show that the company's ITC OS HR is an outlier and favour talquetamab. • Real-world studies show that the company's modelling of talquetamab survival appears optimistic while	~~underestimation of survival of teclistamab recipients~~" Page 187, Section 5.6 "The EAG found that the company's ITC methods are likely to have resulted in potential biases in favour of talquetamab, which transcends to the company's economic model. The key concerns around the company's ITC are: • The ITC does not appear to consider the impact of COVID-19 upon the survival of the unvaccinated MajesTEC-1 population. This would result in an underestimate of teclistamab survival. • ~~Regression studies show that the company's ITC OS HR is an outlier and favour talquetamab.~~ • Real-world studies **are inconclusive in suggesting whether the results of MonumenTAL-1 versus MajesTEC-1 comparison in the company modelling may overestimate the**	statements in the EAG report imply a rejection of the existing OS HR provided in the CS, which was derived based on best available evidence, from a methodologically sound ITC conducted in line with NICE technical support document (TSD) 17.[4] As noted by the EAG in Section 2.2.4, the diagnostic balance of the covariates in the ITC was reasonable with good overlap in the ATT-adjusted distribution of propensity scores between the IPDs of MonumenTAL-1 and MajesTEC-1 and lack of outlier propensity scores. As such, the statements in the EAG report currently allude to preference of lower-grade real-world evidence and/or correlations in PFS and OS HRs obtained from studies which are not applicable to the HRs in the CS, over methodologically robust ITC analyses conducted by the company.	

modelling of teclistamab is pessimistic." **effectiveness of talquetamab** ~~show that the company's modelling of talquetamab survival appears optimistic while modelling of teclistamab is pessimistic~~."			
Issue 1B: Limitations of regression analyses studies chosen to investigate relationship between OS and progression-free survival (PFS) HRs (Section 2.2.7 and Section 3.4.7.3) and use to contextualise the ITC HR pair for talquetamab vs teclistamab			
Section 2.2.7.1 and Section 3.4.7.3 In Section 2.2.7.1 and Section 3.4.7.3, the EAG have presented two studies (Cartier *et al.*[3] and Etekal *et al.*[2]) which performed linear regression analyses depicting the relationship between OS HR and progression-free survival (PFS) HR based on RCTs/phase III studies. Page 91, Section 2.7.1 The EAG noted that "The company submission ITC HR pair for talquetamab versus teclistamab (PFS [redacted], OS [redacted]) is indicated by the black square; it	<u>Remove any discussion of regression analysis studies and how their results may impact the interpretation of the OS and PFS ITC HRs, given the major limitations associated with both studies which invalidate their application to the talquetamab versus teclistamab ITC HRs</u> Please remove Sections 2.2.7.1 and Section 3.4.7.3, as well as all mentions of the regression analysis studies throughout the report.	The discussion of the identified regression analyses in the EAG report should be removed given the strong limitations associated with both Cartier *et al.* and Etekal *et al.*[2, 3] <u>Fundamental differences between the regression studies identified versus the decision problem of this submission</u> • J&J IM have outlined the differences between the regression analysis studies and the CS below, highlighting why these regression analyses are not applicable to the CS based on the criteria outlined by the NICE white paper.[1] In particular, neither study includes any evidence on bispecific antibodies, meaning that they have extremely limited relevance to the comparison between talquetamab and teclistamab that underpins this NICE submission. • **<u>Given these fundamental differences, the regression analyses findings are not</u>**	Comments made are points of disagreement not factual errors. No changes made.

appears to be an outlier relative to the Cartier et al. studies. In TA1015 (teclistamab) HRs for the comparison teclistamab versus Pom-Dex was reported as [redacted] (PFS) and [redacted] (OS) and appears not to be a clear outlier as indicated by the black triangle." Page 91-92, Section 2.7.1 The EAG commented that "When the HR pairs for talquetamab versus teclistamab (black square in Figure 10) and for teclistamab versus Pom-Dex (black diamond in Figure 10) are plotted with the Etekal data. The EAG consider both pairs appear to be outliers particularly that for talquetamab versus teclistamab." Page 92, Section 2.7.1 As such, the EAG claimed that "In		**applicable to the OS and PFS HRs presented in the CS and therefore should be removed.** Cartier *et al.* did not consider novel multiple myeloma (MM) treatments, including BsAbs, with a regression analysis presented based on studies on all lines of therapy, not exclusive to RRMM.[3] • Cartier *et al.* was published in 2015 and considered studies published from 2002 to 2013.[3] • **Differences in population and disease stage:** The regression analysis presented in Cartier *et al.* considered all MM trials regardless of treatment line setting (e.g., 1L) had been included. This means that patients who are not RRMM or TCE RRMM (i.e., patient population of interest in this submission) have been considered in the analysis, making the comparison between Cartier *et al.* and clinical outcomes in a RRMM patient population flawed. • **Differences in interventions and mechanism of action:** The publication of the regression analysis also predates the introduction of novel MM treatments, including BsAbs. Both talquetamab and teclistamab are BsAbs, with their respective trials having commenced in 2018 and 2017, respectively meaning that their trial data were not considered as part of the	

summary, the ITC hazard ratios for OS and PFS for talquetamab appear to be an outlier when compared to previously reported RWE pairs of hazard ratios for multiple myeloma (MM) treatments including treatments for relapsed/refractory multiple myeloma (RRMM). This confirms the EAG concerns pertaining to the magnitude of OS [redacted] for talquetamab relative to teclistamab. The ITC hazard ratio pairs (PFS OS) for teclistamab versus Pom-Dex from TA1015 is more equivocal relative to values from other studies and seemingly a more moderate outsider." The EAG then alluded to "the exploratory analysis of real-world studies (French and German) conducted by the EAG". The appropriateness of		regression analyses.[5, 6] Indeed, as mentioned in TA1015, the introduction of a BsAb like teclistamab resulted in a step-change for survival outcomes in TCE RRMM patients and therefore, it is not unexpected that survival outcomes for BsAbs would differ vastly from that of the older treatment regimens considered in the Cartier *et al.* regression analyses.[7] The novel mechanism by which T cell engagement, activation, and immunological synapse formation lead to the destruction of myeloma cells represents a significant paradigm shift, with implications for immune fitness that extend beyond myeloma progression.[8, 9] • This is a plausible explanation as to why the CS ITC HR pair for talquetamab vs. teclistamab lies outside the other studies considered in Cartier *et al.*[3]. <u>Etekal *et al.* similarly considered trials comparing older treatment regimens with poor survival outcomes and did not include evidence on BsAb treatment regimens</u> • **Differences in intervention and mechanism of action:** Linear regression plots based on RRMM studies were presented separately in Etekal *et al.* However, as noted by Etekal *et al.*, the RRMM trials considered in the regression analyses used older therapies such as proteasome inhibitors, anti-CD38	

the real-world studies chosen by the EAG are commented on below in Issue 1C. The discussion above on the regression analyses is repeated again in Section 3.4.7.3. Page 127, Section 3.4.7.3 "The ITC HR pair for talquetamab versus teclistamab (PFS [redacted], OS [redacted]) is indicated by the black square; it appears to be an outlier relative to the Cartier et al. studies. The 95% credible intervals for the ITC [redacted] OS HR spanned the range 0.36 to 0.71. With an OS HR value between 0.6 and 0.7 (within the ITC 95% credible range) the value ceases to be an outlier according Cartier's regression. The NICE TA1015 HR pair for the comparison teclistamab versus POM-DEX was reported as 0.56 (PFS)		monoclonal antibodies, alkylators and immunomodulatory drugs, and did not include any evidence for BsAbs.[2] A clear caveat was mentioned by Etekal *et al.* themselves cautioning the applicability of the regression analyses to BsAbs, stating the following: **"As no randomised trials have yet [been] reported for other agents such as bispecific agents and chimeric antigen receptor therapy, our results may not be applicable to those settings**."[2] • Given that neither regression publication includes any studies on BsAbs, they are an inappropriate source to base any claims on OS/PFS relationships in BsAbs like talquetamab and teclistamab.[2, 3] • This is additionally supported by the fact that whilst the teclistamab-PomDex ITC HR was not an outlier based on the Cartier *et al.* regression analysis, it was deemed an outlier in the Etekal *et al.* regression analysis. Therefore, it is possible that the fact the HR was not an outlier in the Cartier *et al.* regression analysis is attributable to chance, and the findings remains inconclusive.[2, 3] <u>The EAG report should be updated to remove all mention of the regression analyses, and the resulting uncertainty that the EAG claim to be associated with the ITC HR for talquetamab versus teclistamab</u>	

and 0.52 (OS) and appears not to be a clear outlier as indicated by the black triangle." Page 128, Section 3.4.7.3 "When the HR pairs for talquetamab versus teclistamab (black square) and for teclistamab versus POM-DEX (black diamond) are plotted with the Etekal et al., both pairs appear to be outliers particularly that for talquetamab versus teclistamab. EAG summary, the ITC hazard ratio pair for OS and PFS for talquetamab versus teclistamab appears to be an outliner when compared to previously reported pairs of hazard ratios for MM treatments including treatments for RRMM. The ITC hazard ratio pairs (PFS OS) for teclistamab versus POM-DEX from TA1015 are		• Consequently, given the fundamental limitations of these regression analyses, the EAG report should be updated to remove all mention of these studies to avoid introducing substantial unnecessary and unfounded uncertainty.	

more equivocal relative to values from other studies and seemingly a moderate outsider." Page 14, Executive summary, Table 1 The EAG provided a summary of Issue 3: "The EAG has reservations regarding the reliability of the ITC OS hazard ratio. The EAG investigated a range of alternative HRs to the ITC value ([redacted]) so as to gauge the impact of HR for OS upon the company's economic analysis results." Page 19, Executive summary Given the EAG's concerns with the reliability of the OS ITC HR, the EAG had proposed an alternative approach that "The EAG investigated a range of alternative HRs to the ITC value ([redacted]) so as to gauge the impact of HR			

for OS upon the company's economic analysis results." In Section 3.4.7.3, the EAG presented more details on why the range of alternative HRs would need to be explored, as outlined below. Page 128-129, Section 3.4.7.3 "To bring the ITC OS HR into a Cartier non-outlier range (lower dashed red line) would require a HR of approximately 0.60 to 0.70 rather than [redacted], while to bring the ITC OS HR into a Etekal non-outlier range (lower dashed red line) would require a HR of approximately 0.76 rather than [redacted]. These values are within or almost within the 95% CIs for the ITC OS HR. To fit the regression lines (solid red lines) larger HRs are required."			

Page 26, Executive Summary The results of the range of OS HR explored are presented in Table 5 (page 27, Executive Summary), Table 6 (Page 28, Executive Summary), Table 49 (Page 173, Section 5.1), Table 54 (Page 185, Section 5.5).			
Issue 1C: Limited relevance of RWE studies to UK clinical practice			
Page 17, Executive Summary In the description of Issue 2 of the Executive Summary, the EAG noted that "In the absence of UK data in NHS settings, the EAG performed exploratory analysis using real world studies in European settings to demonstrate the potential impact of talquetamab in routine clinical practice." Page 19, Executive Summary	Please amend the text as follows: Page 17, Executive Summary "In the absence of UK data in NHS settings, the EAG performed exploratory analysis using real world studies in European settings to demonstrate the potential impact of talquetamab in routine clinical practice. **However, the EAG recognise that there are unaccounted differences between European and UK MM treatment landscape and results of this comparison**	There are two major areas of uncertainty associated with the selected European RWE studies: 1. The RWE studies identified do not resolve concerns about the generalisability of the trials to UK clinical practice 2. The EAG have erroneously reported the results of the RWE studies, which when corrected will change the EAG's initial conclusions These issues are discussed in greater detail in the paragraphs below. The EAG report does not currently reflect any of these uncertainties and therefore presents an inaccurate and misleading representation of the usefulness of these studies, and the conclusions drawn from them relating to the overall magnitude of survival benefit for talquetamab derived based on robust trial vs. trial comparison	Comments made regarding uncertainty of RWE are points of disagreement not factual errors. However, given the incorrect figures described in 1a above **EAG entire updated 3.4.7.2 Section.**

This is mentioned again in the description of Issue 3 of the Executive Summary (Page 19) wherein the EAG justified that "Scenarios could be conducted based upon the recent real world European studies (France and Germany) of talquetamab and teclistamab. EAG additional analysis demonstrate that OS for talquetamab compared to teclistamab from the CS ITC is an outlier compared to these real-world studies. Such analyses may be more relevant to the UK than the resulted from multinational MajesTEC-1 and MonumeTAL-1 that were almost devoid of patients from the UK." Page 44-45, Section 2.1.3.1.1 The EAG commented that "supportive direct comparative evidence in	**need to be treated with caution.**" Page 19, Executive Summary "Scenarios could be conducted based upon the recent real world European studies (France and Germany) of talquetamab and teclistamab **but are not generalisable to UK clinical practice or the decision problem of this submission**. ~~EAG additional analysis demonstrate that OS for talquetamab compared to teclistamab from the CS ITC is an outlier compared to these real-world studies. Such analyses may be more relevant to the UK than the resulted from multinational MajesTEC-1 and MonumeTAL-1 that were almost devoid of patients from the UK.~~ Page 44-45, Section 2.1.3.1.1 "The EAG conducted exploratory analysis of the efficacy of talquetamab using observational studies (Real World Evidence in non-UK settings [RWE]) to investigate plausible efficacy estimates for talquetamab,	and best available evidence, in line with NICE TSD17.[4] It is important that the EAG report is amended as specified on the middle column, to ensure that a factually accurate and balanced representation of these studies is presented throughout the report. 1. <u>The RWE studies identified do not resolve concerns about the generalisability of the trials to UK clinical practice and represent a lower grade of evidence compared to trial evidence</u> Throughout the EAG report, the EAG have incorrectly referenced the lack of UK patients in the trials. This in an error that has been flagged as part of this FAC, as patients from the UK were enrolled in the MajesTEC-1 trial. Irrespective, given that the RWE studies selected by the EAG are in European settings and therefore would be representative of the treatment pathway in their respective countries rather than the UK, the consideration of non-UK RWE fails to resolve the EAG's concern regarding the generalisability of MonumenTAL-1 to UK clinical practice. This has been commented on as part of Issue 10. Without any proper adjustment of treatments which are not available in the UK and other differences in MM treatment such as prophylactic use of IVIg, etc., the results of the non-UK RWE cannot be directly compared with the data presented in the CS and are not more generalisable to the UK than	

NHS populations is lacking. The EAG conducted exploratory analysis of the efficacy of talquetamab using observational studies (Real World Evidence in non-UK settings [RWE]) to investigate the plausible true efficacy of talquetamab (see Section 3.3.6)." Page 92, Section 2.7.1 After presenting the regression analyses as outlined above in Issue 1B, the EAG commented that "The exploratory analysis of real-world studies (French and German) conducted by the EAG suggests that the results of MonumenTAL-1 versus MajesTEC-1 may overestimate the effectiveness of talquetamab". Details on the real-world studies used in further extrapolation by the EAG	**however it is acknowledged that given that none of the studies were UK-based similar limitations apply to these sources**". Page 92, Section 2.7.1 "The exploratory analysis of real-world studies (French and German) conducted by the EAG **are inconclusive in suggesting whether**~~suggests~~ ~~that~~ the results of MonumenTAL-1 versus MajesTEC-1 may overestimate the effectiveness of talquetamab". A correction to Figure 27 is required, as follows: Page 124, Section 3.4.7.2 The EAG have incorrectly overlaid the teclistamab PFS KM curve from MajesTEC-1 with the Perrot *et al.* OS KM curve. The MajesTEC-1 OS KM curve should be used instead in Figure 27. A corresponding amendment to the text is then required, as follows:	MonumenTAL-1 and MajesTEC-1. For example, the trial data presented in the CS have been adjusted to account for subsequent treatments which are not available in the UK, representing evidence which is more reflective of UK clinical practice than the non-UK RWE data. As outlined by the NICE methods for health technology evaluations (PMG36), a clear preference for non-randomised studies is stated in the absence of RCT evidence, to form the primary source of evidence.[13] As per the NICE RWE framework, real-world data are meant to fill evidence gaps and RWE studies are required to use "fit-for-purpose" data which none of the identified RWE studies have adequately addressed or utilised (see detailed reasons below).[14] Additionally, the ITC performed in the CS (Section 2.10) was conducted in line with TSD17 guidance based on best available evidence (utilising IPD for both trials); the use of RWE represents a lower grade of evidence that is associated with additional uncertainty.[4] 2. Selective and inaccurate reporting of results from the selected RWE studies The EAG identified three RWE studies (Perrot, Riedhammer and Frenking), suggesting that these may be more relevant to the UK than the clinical trials for talquetamab and teclistamab. Beyond the generalisability concerns associated with these studies, the EAG's reporting of the selected RWE	

are presented in Section 3.4.7.2. In summary, "[t]hree studies were identified by the EAG: two on teclistamab from Germany[10] and from France on teclistamab[11]; and one on talquetamab from Germany[12]. Maximum follow up in the studies was 15 months, the German studies included 122[10] and 131 patients[12], the French study 312[11]." Teclistamab (German RWE [Riedhammer *et al.*[10]] and French RWE [Perrot *et al.*[11]]) Page 124, Section 3.4.7.2 The EAG claimed that "Both German and French real-world teclistamab studies exhibit superior OS relative to the company KM (see Perrot et al (black line) company (red line) and Riedhammer	"Both German and French real-world teclistamab studies **are inconclusive in demonstrating whether superior OS results are suggested by real-world studies** ~~exhibit superior OS~~ relative to the company KM (see Perrot et al (black line) company (red line) and Riedhammer (red line) company (black line) in Figure 27" Page 125, Section 3.4.7.2 The EAG further noted that "In both real-world studies, visual inspection suggests the PFS plots are similar to the company KM. **The real-world studies are inconclusive in suggesting whether superior OS outcomes are observed in real-world for teclistamab compared to MajesTEC-1**~~This contrasts the plot for OS shown in ; as there appears to be a relative lack of correspondence in the submitted PFS and OS KMs compared with the two real world studies~~." Page 126, Section 3.4.7.2	studies is inaccurate and misleading, with several concerns detailed below: ***I. Incomplete reporting of median OS and PFS data in RWE studies*** The EAG did not report median OS/PFS values for the identified studies; however, these should be presented in the relevant section of the EAG report for clarity on the outcomes presented in the RWE studies. **Study on teclistamab** / **Median PFS (months)** / **Median OS (months)** / **Follow-up period (months)** MajesTEC-1[6] / 11.4 / 22.2 / 30.4 Perrot[11] / 11.3 (95% CI: 8.9, 14.9) / 17 (95% CI: 13.8, NA) / 11.9 Riedhammer[10] / 8.7 (95% CI: NR) / NE / 5.5 As illustrated above, both RWE studies on teclistamab report different survival outcomes, and their robustness is extremely limited, based on their substantially shorter follow-up period in comparison to MajesTEC-1.[10, 11] ***II. Incorrect reporting of OS outcomes in Perrot et al. and limitations associated***	

(red line) company (black line) in Figure 27" Page 125, Section 3.4.7.2 The EAG further noted that "In both real-world studies, visual inspection suggests the PFS plots are similar to the company KM. This contrasts the plot for OS shown in ; as there appears to be a relative lack of correspondence in the submitted PFS and OS KMs compared with the two real world studies." <u>Talquetamab (French RWE [Frenking *et al.*[12]])</u> Page 126, Section 3.4.7.2 The EAG noted "Figure 29 compares the reconstructed KM plots (95% CI) with the company submitted KM plots for talquetamab. These suggest superior OS and PFS for the CS	The EAG noted "Figure 29 compares the reconstructed KM plots (95% CI) with the company submitted KM plots for talquetamab. These suggest superior OS and PFS for the CS relative to real-world use of talquetamab. **However, the patient population in Frenking *et al.* was more heavily pre-treated with a higher number of median lines of therapy of 6 and included patients who had received prior CAR-T cell therapy (34%) and patients who have received prior BsAb (20%). The Frenking *et al.* patient population is therefore comparatively less reflective of UK clinical practice than MonumenTAL-1 given that patients do not receive CAR-T cell therapy in the UK.**" Page 126, Section 3.4.7.2 The EAG noted that "As such, relative to real-world usage **in Europe (Germany and France)**, the CS seems to suggest over optimistic OS and PFS ~~t~~estimates for talquetamab **with inconclusive results for**	***with RWE studies (i.e., limited follow-up period and non-UK setting)*** Of particular importance, the EAG have stated that the Perrot study had superior OS relative to MajesTEC-1. This is factually incorrect. **<u>The EAG have incorrectly overlaid the MajesTEC-1 PFS KM data instead of the OS KM data in Figure 27.</u>** As shown in the comparison above, the MajesTEC-1 trial demonstrated improved OS outcomes compared to the Perrot study (based on a naïve comparison of median OS). Whilst median OS was not reached in Riedhammer, this study has a significantly short follow-up period of 5.5 months and therefore is associated with greater uncertainty and comparison of outcomes from this study with MajesTEC-1 trial data with substantially longer follow-up is not appropriate. **<u>J&J IM have provided the correct OS KM curves for teclistamab in Appendix A i.e., the Perrot and Riedhammer studies have been overlaid with the OS KM curve from MajesTEC-1.</u>**. Overall, the RWE studies have markedly shorter follow-up durations with immature results (e.g. Riedhammer *et al.*) and therefore need to be interpreted with caution when compared with MajesTEC-1 data, which has a much longer follow-up duration. Moreover, as highlighted by J&J IM above, these RWE studies are outside of the UK and therefore, are not reflective of UK clinical practice. Concerns with the underestimation of the teclistamab efficacy data on these grounds as	

relative to real-world use of talquetamab." <u>Comparison of real-world studies with trial data</u> Page 126, Section 3.4.7.2 The EAG noted that "As such, relative to real-world usage, the CS seems to suggest over optimistic OS and PFS estimates for talquetamab while, in contrast, an over pessimistic estimate for teclistamab OS." Page 134, Section 3.4.7.5 The EAG noted the following: "An evidence base for the opinion-led predictions is difficult to identify or envisage in absence of evidence other than that from MonumenTAL-1 and MajesTEC-1 that is included in the CS.	**teclistamab OS** ~~while, in contrast, an over pessimistic estimate for teclistamab OS~~. **However, the EAG acknowledge that there are differences between the European and UK MM treatment landscape. These differences have not been accounted for in the EAG comparison of the survival outcomes for teclistamab and talquetamab, and therefore, represents a major limitation.**" Page 134, Section 3.4.7.5 "An evidence base for the opinion-led predictions is difficult to identify or envisage in absence of evidence other than that from MonumenTAL-1 and MajesTEC-1 that is included in the CS. ~~However, in this context,~~ **tThe** recent publication of three real-world studies from Germany[10] and France[11] **do not adequately mitigate** ~~to some extent mitigates~~ this deficiency **given the incongruent outcomes reported across the teclistamab real-world studies**	proposed by the EAG are not sufficiently substantiated by these RWE studies. ***III. Heavily pre-treated population in Frenking et al. (RWE study for talquetamab) compared to both MonumenTAL-1 and UK clinical practice resulting in underestimation of talquetamab efficacy in Frenking et al.*** The EAG only identified one non-UK RWE study for talquetamab by Frenking *et al.* However, this study has a short median follow-up of 8 months compared to the longer follow-up duration of MonumenTAL-1 (Cohort C; 31.2 months at the September 2024 DCO).[15] Moreover, Frenking *et al.* includes a heavily pre-treated population (median: 6; compared to MonumenTAL-1 Cohort C [September 2024 DCO]: 4.5), and importantly, patients who have received prior CAR-T cell therapy (34%) and patients who have received prior BsAb (20%).[16] Hence, the patients considered in the Frenking *et al.* study are not representative of UK clinical practice, and any resulting claims of an overestimation of talquetamab efficacy in MonumenTAL-1 data cannot be substantiated. <u>Conclusion</u> Considering the substantial uncertainties associated with these RWE studies, it is important that the EAG report is amended in line with the changes requested in the middle column. Without these changes, the EAG's write-up of these studies, and	

However, in this context, the recent publication of three real-world studies from Germany[10] and France[11] to some extent mitigates this deficiency and suggests that in practice talquetamab may perform less well relative to teclistamab than is suggested by the company's lognormal-based modelling."	**and the more heavily pre-treated and CAR-T exposed patient population in the talquetamab real-world study**~~and suggests that in practice talquetamab may perform less well relative to teclistamab than is suggested by the company's lognormal-based modelling~~."	conclusions relating to the treatment effect for talquetamab versus teclistamab, are misleading and do not present a balanced viewpoint considering the totality of the available evidence.	

Issue 2 Inappropriate assumption of equal intravenous immunoglobulin (IVIg) use and link between IVIg and survival rates for teclistamab and talquetamab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 2A: Inappropriate link between IVIg use and survival and/or infection rates			
Page 22, Executive Summary (Description of Issue 5) "The EAG assume IVIg is used to mitigate effects of infection and is only received by live patients. Therefore, IVIG use will depend on infection rate and the proportion remaining alive.	Remove all mention of the main drivers of IVIg usage being explicitly linked to the survival of patients or rates of infection in all relevant places in the EAG report, including but not limited to the sections below: • Executive Summary (Page 22) • Section 3.4.10.4 (Page 143)	The EAG's approach of using percentages of all-grade infection (71% in MonumenTAL-1 vs [redacted]% in MajesTEC-1) and survival rates (61% in MonumenTAL-1 at ~40 months and [redacted]% in MajesTEC-1) alone on which to anchor the appropriate level of IVIg use is an oversimplification of a complex and multifactorial clinical consideration.	Comments made are points of disagreement not factual errors.

The EAG disagree with the company for the following reasons: a] At cut-off (after about 40 months) 71% of Cohort C have had an infection while at 36 months 61% are still alive and can receive IVIg. In contrast at MajesTIC-1 cut off [redacted]% have had an infection but only [redacted]% are still alive to receive IVIg. It is evident that there will be more use of IVIg in the talquetamab arm than in the teclistamab arm over the first ~40 months. b] Beyond 40 months there is likely to be continued use of IVIg. At 15 years, only about 3% of the teclistamab arm remain alive compared with 19% of talquetamab arm. It is evident that beyond 15 years IVIg usage will be greater in the talquetamab arm than the teclistamab arm, because few	• Section 3.4.12 (Page 151) • Section 4.4 (Page 168–170 [Table 48]) • Section 5.6 (Page 187–188) The EAG report should be amended to remove the factually incorrect assumption that IVIg usage should be explicitly linked to survival rates and/or infection rates. Alternatively, these sections should be rewritten to more broadly discuss all of the potential factors that may relate to IVIg usage.	This is reflected by the heterogeneous clinical guidelines published in the literature on the use of IVIg therapy in patients receiving bispecific antibodies.[17] The literature highlights the use of IVIg is multifactorial and influenced by survival rates, the risk and severity of infections, and the number of previous infections. Severity of infections is particularly important to consider, given the difference in Grade 3/4 infections between MajesTEC-1 ([redacted]%) and MonumenTAL-1 ([redacted]%) respectively. Additionally, IVIg usage is contingent on various other elements, such as the specific treatment patients are receiving and the interactions between its mechanism of action, the drug target, and the patient's immune system. With bispecific antibodies specifically, IVIg use is intrinsically linked to whether the treatment targets BCMA	

in the teclistamab arm are alive to receive IVIg. c] Real world studies from France and Germany suggest that prophylaxis with IVIg may be routine in practice to mitigate against infections in immune-compromised patients that would lead to interruptions in the use of effective therapies. The EAG considers this would be the likely case in UK practice. Because the submission models more patients survive in the talquetamab arm than the teclistamab arm this infers greater routine use of IVIg in the talquetamab arm" Page 143, Section 3.4.10.4 The EAG commented that "Furthermore, the EAG considers that the company's approach to modelling IVIg usage as a one-off cost underestimates IVIg costs in favour of talquetamab."		or GPRC5D. IVIg usage in MonumenTAL-1 ([redacted]%) was significantly reduced when compared to both teclistamab in MajesTEC-1 ([redacted]%) as well as elranatamab, another BCMA BsAb, in MagnestisMM-3 (43.1%). This clearly indicates the difference in IVIg usage for B cell maturation antigen (BCMA)-targeted bispecific antibodies versus talquetamab. Therefore, the EAG's statements that patients receiving talquetamab are anticipated to have increased IVIg use owing to the associated OS benefit over teclistamab, are therefore fundamentally flawed, and at odds with the available evidence base. There is both empirical evidence based on trial data and mechanistic reasons (i.e., BCMA-targeting vs. GPRC5D targeting) that contradict the EAG's assumptions. Finally, whilst it is acknowledged that a small proportion ([redacted]%) of patients receiving talquetamab will subsequently receive teclistamab, this does not provide any sufficient	

Page 151, Section 3.4.12 The EAG commented that “In the absence of submitted relevant evidence the EAG assumes that IVIg use is undertaken to mitigate effects of infection. Since it can only be received by live patients the main drivers of IVIg usage will be the amount of infection and the survival of patients”. Page 168-170, Section 4.4, Table 48 “In the absence of submitted relevant evidence the EAG assumes that IVIg use is undertaken to mitigate effects of infection. Since it can only be received by live patients the main drivers of IVIg usage will be the amount of infection and the survival of patients. At data cut-off (after about 40 months) 71 % of Cohort C had had an infection (Table 49) and at 36 months (Table 29) 61% were still alive and able to receive IVIg, while at MajesTEC-1 at data cut off [redacted]%		rationale to assume that IVIg usage should be explicitly linked with survival, given that the majority of patients receive other subsequent treatments which are unlikely to be associated with concomitant IVIg administration.	

had had an infection and only [redacted]% were still alive (Figure 27). From these data, the EAG concludes that in the relatively short term (3.5 years) IVIg usage would be greater for talquetamab recipients (Cohort C) than for teclistamab recipients. Beyond 40 months, infections are unlikely to cease, and IVIg use would not be precluded; there is likely to be continued use of IVIg (at 40 months). Since the company model shows that by 15 years (Figure 27) only about [redacted]% of teclistamab arm remain alive compared with [redacted]% of talquetamab (Cohort C) arm, the EAG concludes that use of IVIg would be greater for talquetamab arm than for teclistamab arm patients irrespective of any subsequent treatments they may or may not receive. The EAG concludes that company's submitted evidence			

indicates there will be substantially more use of IVIg for talquetamab arm patients than for teclistamab arm patients, and that this should reflected in some way the economic analysis. Furthermore, real world studies from France[11] and Germany[10, 12] suggest that prophylaxis with IVIg may be routine in practice to mitigate against infections in immune-compromised MM patients and to avoid interruptions in the use of effective MM therapies. In the absence of data, we assumed that the proportion of people receiving IVIg with subsequent teclistamab to be consistent with those receiving IVIg with initial teclistamab treatment ([redacted]). People receiving subsequent teclistamab treatment were assumed to receive nine IVIg doses, i.e., the same number of IVIg doses as initial teclistamab treatment and in line with the duration that			

people received subsequent teclistamab. Additionally, people receiving subsequent talquetamab treatment were assumed to receive six IVIg doses. This is in line with the duration that people received subsequent talquetamab." Page 187, Section 5.6 "Another potential bias in favour of talquetamab is IVIg usage not fully/appropriately captured in the company's model. The EAG assumes that IVIg is used to mitigate the effects of infection and is only received by people that are alive. Based on the evidence submitted, it is evident that there will be more IVIg usage in people receiving talquetamab compared to teclistamab over the first 40 months." Page 188, Section 5.6 "However, given the reservations of the company's ITC HR, and the challenges of			

re-analysis without individual patient data (IPD), our preference was to undertake scenarios to assess the impact to the incremental cost effectiveness ratio (ICER) by increasing the hazard ratio. Additionally, in the absence of better evidence on IVIg usage and lack of functionality in the model to implement IVIg usage depending on infection rate and proportion alive, the EAG opted for a conservative approach in scenario analysis to assume that IVIg use to be equal in both arms."			
Issue 2B: Inappropriate assumption of equal IVIg use for teclistamab and talquetamab (EAG model scenario 2)			
Page 15, Executive Summary, Table 1 In the summary of Issue 5, the EAG noted that "The company economic model assumes greater use of IVIg use in the teclistamab arm than in the talquetamab arm. The costs deriving are therefore greater	<u>Remove the scenario assuming equal IVIg use for both talquetamab and teclistamab presented in the EAG report. This includes, but is not limited to reporting of the scenario of the following sections of the EAG report:</u> • Executive Summary (Page 15 [Table 1], 16, 22, 23, 26 [Table 5], 28 [Table 6]) • Section 5.1 (Page 173, Table 49)	This scenario is inappropriate and should be removed for the following reasons: • As noted in response to issue 2A above, IVIg use is intrinsically linked to the bispecific treatment that a patient receives, and whether it targets BCMA or GPRC5D. This is demonstrated by the fact that IVIg usage for talquetamab in	Comments made are points of disagreement not factual errors.

in the teclistamab arm than the talquetamab arm. In scenario analysis, the EAG assumes equal use of IVIg in both talquetamab and teclistamab." Page 16, Executive Summary "The modelling assumptions that have the greatest effect on the ICER are: • Talquetamab versus teclistamab OS hazard ratio (HR) • Talquetamab versus teclistamab time-to-treatment discontinuation (TTD) • Equal use of intravenous immunoglobulin (IVIg) treatment between both arms. i.e., assumed that [redacted]% of people in the teclistamab cohort start IVIg treatment" Page 22, Executive Summary As part of the alternative approach suggested by the	• Section 5.5 (Page 185, Table 54) As outlined in the right-hand column, an assumption of equal IVIg use for both talquetamab and teclistamab is inappropriate and directly contradicts the data available from the respective principal trials for teclistamab and talquetamab, the published literature on GPCR and BCMA BsAbs, and an unanimously held view by all clinical experts consulted by the Company, and is therefore in no way reflective of clinical reality. As such, this scenario should be removed from the EAG report.	MonumenTAL-1 ([redacted]%) was significantly reduced when compared to both teclistamab in MajesTEC-1 ([redacted]%) as well as elranatamab in MagnestisMM-3 (43.1%). • This clearly indicates the difference in IVIg usage for BCMA-targeted bispecific antibodies versus talquetamab. • Clinical experts consulted by the company also unanimously agreed that talquetamab is expected to reduce the need for supportive IVIg treatment compared with teclistamab. • This is further supported by a 2023 meta-analysis (Reynolds, *et al*) of 16 clinical trials which showed that the rate of Grade ≥3 infections is significantly higher with BCMA-targeting BsAbs compared with non-BCMA-targeting BsAbs.[18] • The higher rate of infections will subsequently lead to a greater IVIg use requirement	

EAG for Issue 5, the EAG noted “In the absence of better evidence in scenario analysis the EAG assumes equal use of IVIg in both arms. The EAG acknowledge that this is a conservative approach that will tend to favour talquetamab in the economic analysis.” Page 23, Executive Summary As part of the additional evidence or analyses that might help to resolve this key issue, the EAG noted “Scenarios could be conducted in which costs allocated to the use of IVIG are related more directly to survival than in the company’s base-case.” Page 26, Executive Summary, Table 5 The EAG listed Scenario 1 “Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment”		for patients receiving BCMA-targeting BsAbs. • Consequently, this scenario analysis directly contradicts the totality of the available evidence, which indicates that treatment with talquetamab is associated with reduced IVIg use versus teclistamab. • Furthermore, amending the proportion of patients receiving IVIg use in the teclistamab arm is inappropriate, as this only alters the costs in the ICER equation. The efficacy data available have not and cannot be accurately adjusted in any reasonable way to account for the impact of reduced IVIg usage compared to the level reported in MajesTEC-1. o The inappropriateness of only adjusting for costs associated with IVIg usage and not efficacy outcomes was specifically highlighted by the EAG in TA1015.[7]	

Page 28, Executive Summary, Table 6 The EAG listed Scenario 2 "Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment" Page 173, Section 5.1, Table 49 The EAG listed Scenario 1 "Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment" Page 185, Section 5.5, Table 54 The EAG listed Scenario 2 "Equal use of IVIg treatment between both arms. I.e., assumed that [redacted]% of people in the teclistamab cohort starting IVIg treatment"		○ Given that IVIg manages infections and therefore its use is intrinsically associated with a reduction in infection-related mortality, reducing the proportion of teclistamab patients receiving IVIg would naturally be linked with an associated reduction in OS outcomes. By reducing IVIg usage only and not adjusting for corresponding efficacy outcomes, this scenario is highly likely to be biased in favour of teclistamab. In conclusion, the EAG's scenario which assumes equal proportions of IVIg use in patients receiving teclistamab and talquetamab is clinically inappropriate based on the difference in the drugs mechanisms of action and the totality of evidence which suggests that talquetamab will require less IVIg versus teclistamab. Additionally, the scenario does not	

		accurately capture the impact of the assumption on the company's ICER as it only adjusts costs (and not benefit) in the ICER equation resulting in misleading results that are likely biased in favour of teclistamab. Based on these grounds the scenario is inappropriate and inaccurate and should be removed from the EAG report.	
Issue 2C: IVIg use in RWE studies for talquetamab and teclistamab			
Page 143, Section 3.4.10.4 The EAG state that "This is supported by the RWE studies from Germany and France which showed that patients on talquetamab were on treatment for a longer duration compared to patients on teclistamab and required more IVIg.".	Please amend the text as follows: "~~This is supported by~~ **However** the RWE studies from Germany and France ~~which~~ showed that a **higher proportion of patients receiving teclistamab required IVIg** ~~patients on talquetamab were on treatment for a longer duration compared to patients on teclistamab and required more IVIg~~."	This statement should be updated to avoid misinterpretation and improve the factual accuracy of the statement. The RWE studies show that a higher proportion of patients on teclistamab received IVIg than talquetamab, and this should be accurately reflected in the statement. In addition, the referenced studies do not give data on length of time on treatment for teclistamab or talquetamab and therefore time on IVIg cannot be derived.	We have amended the statement on page 145, which now reads, *However, the real-world studies from Germany and France showed that a higher proportion participants received teclistamab required IVIg.*

Issue 3 Inaccurate description of the company's approach to modelling long-term estimates for teclistamab and talquetamab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 3A: Incorrect description of modelling long-term estimates for teclistamab			
Page 20–21, Executive Summary, Issue 4; Page 108–117, Section 3.4.6; Page 167–172, Section 4.4 and Page 187–188, Section 5.6 The EAG inaccurately describes the derivation of the long-term estimates for both talquetamab and teclistamab. The inaccuracies	Please amend the text as follows: Page 20-21, Executive Summary "To bring lognormal OS and PFS teclistamab models into a plausible range on extrapolation the models were forced to follow a pre-determined trajectory from 5 to 15 years~~, followed by hazard adjustment from 15 years to lifetime extrapolation~~." Page 134, Section 3.4.7.5 The EAG describe that "The resulting	As detailed in Section 3.3 of the CS, between Year 5–15 in the economic model the lognormal curves were calibrated to align with clinical expert estimates for survival at 10 and 15 years. After Year 15, lognormal hazards were applied to the teclistamab extrapolation, resulting in the flattening of the curve. As is standard practice in oncology models, the long-term overall survival extrapolation was also capped by the general population lifetables throughout the model time horizon, to ensure that the per-cycle hazard of death was never lower than the corresponding hazard of death in the general population.	Amended as requested.

for the description of the teclistamab modelling approach are covered within this row. The inaccuracies for the description of the talquetamab modelling approach are outlined in issue 3B below. In the respective sections as outlined above, the EAG described the teclistamab modelling approach for OS, PFS and	models consist of three 5-year phases a], b], c], followed by an extended extrapolation from 15 to 40 years. Phase a] extends over years 0 to 5, seven parametric models (with no adjustment) were fit to teclistamab KM plots, these “phase a]” models differ little from one another over this short period. “Phase b]” extends from 5 years to 10 years and all model trajectories are made to converge on the 10-year specified value (10% at 10 years for teclistamab OS), the resulting difference between models diminishes over this period until at 10 years they all reach the same value. “Phase c]” extends		

TTD, as follows: Page 20-21, Executive Summary “To bring lognormal OS and PFS teclistamab models into a plausible range on extrapolation the models were forced to follow a pre-determined trajectory from 5 to 15 years, followed by hazard adjustment from 15 years to lifetime extrapolation.” Page 134, Section 3.4.7.5	from 10 to 15 years and all parametric models are forced to follow almost identical trajectory to adhere to clinical prediction. Beyond 15 years, **lognormal hazards were applied to the teclistamab curves and the model is capped to ensure that the per-cycle hazard of death cannot be lower than the corresponding hazard in the general population. The time horizon extends** ~~extending~~ to 40 years over a time that 3.5% discounting has increasing influence, increasing hazard dependent on the individual parametric used.”		

The EAG describe that "The resulting models consist of three 5-year phases a], b], c], followed by an extended extrapolation from 15 to 40 years. Phase a] extends over years 0 to 5, seven parametric models (with no adjustment) were fit to teclistamab KM plots, these "phase a]" models differ little from one another over this short period. "Phase b]" extends from 5 years to 10			

years and all model trajectories are made to converge on the 10-year specified value (10% at 10 years for teclistamab OS), the resulting difference between models diminishes over this period until at 10 years they all reach the same value. “Phase c]” extends from 10 to 15 years and all parametric models are forced to follow almost identical trajectory to adhere to			

clinical prediction. Beyond 15 years, extending to 40 years over a time that 3.5% discounting has increasing influence, increasing hazard dependent on the individual parametric used."			
Issue 3B: Incorrect description of modelling long-term estimates for talquetamab			
Page 20, Executive Summary, Issue 4; Page 108–117, Section 3.4.6; Page 167–172, Section 4.4 and Page 187–188, Section 5.6	The EAG should update the Executive Summary Issue 4, Section 3.4.6, Section 4.4 and Section 5.6 accordingly to correctly explain how the talquetamab extrapolations were derived from the Committee-accepted	The EAG report does not correctly capture the Company's approach to modelling of long-term survival estimates for talquetamab, as described in Section 3.3 of the CS. All relevant sections of the EAG report should therefore be updated to ensure the description of the modelling approach is factually accurate. As detailed in Section 3.3 of the CS, the teclistamab curve (in line with the approach accepted by NICE in TA1015) has a two-stage adjustment and calibration applied to it to ensure OS 10- and 15 year OS estimates were aligned with clinician estimates.[7] In TA1015, the survival curves were ATC weighted to the UK RW TCE cohort study, before they were extrapolated using the LogNormal distribution and calibrated to clinician estimates.[7]	Amended as appropriate without altering EAG arguments.

The EAG inaccurately describes the derivation of the long-term estimates for both talquetamab and teclistamab. The inaccuracies for the description of the teclistamab modelling approach are outlined above in issue 3A.	teclistamab curves in TA1015.[7] This includes, but is not limited to, correcting the following key points: • The HRs applied to the respective OS, PFS and TTD teclistamab curves to generate the respective talquetamab curves did <u>not</u> differ following 15 years in the model • The talquetamab curves were derived from the calibrated teclistamab curves accepted for decision	The talquetamab curve is derived from the respective teclistamab curves (ATC weighted to the MonumenTAL-1 Cohort C patient population) by applying the HRs for OS (post subsequent treatment adjustment), PFS and TTD from the ITC comparing talquetamab vs. teclistamab (detailed in Section 3.3 of the Company submission) to the respective OS, PFS and TTD curves accepted by NICE in TA1015.[7] <u>The resultant talquetamab extrapolations after applying the ITC HRs to the calibrated ATT-weighted teclistamab extrapolations were then capped for GPM</u>	

	making in TA1015.[7] • Talquetamab OS extrapolations were capped by general population mortality, as is standard practice in in oncology modelling.		
Page 110–113, Section 3.4.6.1, Figures 12–14 J&J IM are unclear on where Figures 12–14 and Figure 16 have been sourced from and generated.	As noted above, the EAG should update Section 3.4.6 of the EAG report to accurately reflect the modelling approach for talquetamab. Figures 12–14 and Figure 16 are incorrect and should be removed.	The current description of the talquetamab modelling approach has been misinterpreted by the EAG and should be clarified. This should be updated to ensure the modelling approach is correctly detailed in the EAG report and the correct figures are displayed. In Figure 12 and Figure 16 specifically, the LogNormal curve presented by the EAG is incorrect (as can be seen by the poor fit to the KM data). J&J IM have provided a plot below showing the unadjusted OS extrapolation (post-subsequent treatment adjustment) using a lognormal fit, without the application of a GPM cap (the purple curve). The blue curves show this extrapolation with the GPM cap applied, while the pink curve is the base case talquetamab curve derived using the HR approach detailed in the CS, Section 3.3.	Figures 12-14 and 16 were generated by the EAG. We have amended the Figure captions accordingly to demonstrate the exploratory nature of these charts.

		Figure 1: Corrected versions of the talquetamab OS extrapolation, before and after the application of calibration and general population mortality 	EAG note: Fig 12; the fit to the KM is good and nearly the same for all models shown. The only parting is at the small tail to the KM. The plots have same fit as shown in submission Fig 34. Fits to the talquetamab OS KM are anyway immaterial to the economic modelling since (as stated by the EAG), the talquetamab modelling is based on the Teclistamab lognormal model.

			Regarding the KM for teclistamab, the only model provided in the submission text document was submission Figure 27 that shows a post two stage extrapolation to 15 years and is identical to the EAG Figure 16 adjusted LN curve to 15 years. No other curves fit to teclistamab KM were presented in the submission text document. Evidence provided as FAC are not considered.

Page 111, Section 3.4.6.1 The EAG states; "As shown in the economic model all these parametric models, even the Gompertz model, can be forced into plausibility by the company adjustment method (Figure 15)."	Please amend the text as follows: "As shown in the economic model all these parametric models, even the Gompertz model, can be forced into plausibility by ~~the company adjustment method~~ **applying GPM capping** (Figure 15).".	The current description of the talquetamab modelling approach has been misinterpreted by the EAG and should be clarified. No further adjustment beyond applying GPM capping was applied.	We have amended for clarity on page 113.

Issue 4 Clarification of the confounding of OS from deaths due to non-cancer causes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, Section 2.2.5.1.5 The EAG note that "Moreover, since OS as an outcome considers all-cause mortality, it may be confounded by	J&J IM request that this statement is removed from the EAG report.	This is a factual inaccuracy - deaths due to COVID-19 are not necessarily "non-cancer" related. If patients have an increased risk of infection with BCMA-targeting bispecific	Comments made are not factually inaccurate. EAG statements are based on company's definition as

deaths due to non-cancer causes (e.g., COVD-19), potentially obscuring the true survival benefit of any given treatment.”.		antibodies, such as teclistamab, when compared to talquetamab (as shown in the naïve comparison in the CS), and infection-related mortality is higher with teclistamab than talquetamab (as demonstrated in Section 2.11.5 of the CS), then deaths due to COVID-19 arguably are inherently linked to patients’ cancer treatment, especially given the evidence that teclistamab can severely impair humoral immunity and vaccination responses.[9] This statement should therefore be removed as it is factually inaccurate.	provided in the teclistamab company submission.

Issue 5 Incorrect statements regarding the number of UK patients enrolled in MajesTEC-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Executive Summary The EAG have incorrectly noted that “There were no UK patients in the trial evidence for the intervention (Talquetamab, MonumenTAL-1) and only one for the	Please amend the text as follows: “There were no UK patients in the trial evidence for the intervention (Talquetamab, MonumenTAL-1) **but a total of [redacted] patients were enrolled in the comparator trial** ~~and only one for the comparator~~ (Teclistamab, MajesTEC-1)”.	The MajesTEC-1 study included a total of nine patients across three study sites in the UK. These data are available in the August 2023 Clinical Study Report (CSR) for MajesTEC-1, shared as part of the reference pack of the CS. As such, the	Corrected on all pages.

comparator (Teclistamab, MajesTEC-1)." This factual inaccuracy is repeated multiple times across the EAG report (e.g., Page 14, Page 55, Section 2.2.1.3, Page 95, Section 2.4) and should be rectified accordingly at each mention.		statement that no UK patients were included in the MajesTEC-1 study is factually inaccurate.	
Page 19, Executive Summary When describing some RWE on teclistamab and talquetamab the EAG states; "Such analyses may be more relevant to the UK than the resulted from multinational MajesTEC-1 and MonumeTAL-1 that were almost devoid of patients from the UK."	Please amend the text as follows: "Such analyses may be more relevant to the UK than the **resultant** from multinational MajesTEC-1 and MonumenTAL-1. **The MonumenTAL-1 trial did not include any patients from the UK, whilst a total of nine patients from the UK were enrolled in MajesTEC-1**".	The typographical error should be corrected to improve clarity. Furthermore, as the MajesTEC-1 trial included a non-insignificant number of UK patients; to enable accurate interpretation, the sentence should be updated to more accurately reflect the number of patients enrolled in the respective trials.	Amended for clarity.

Minor Issues (Ordered Chronologically)

Issue 6 Additional wording required to clarify assumptions in the EAG model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Executive Summary "The modelling assumptions that have the greatest effect on the ICER are:"	Please amend the text as follows: "The modelling assumptions **in the EAG model** that have the greatest effect on the ICER are:"	It is unclear that the modelling assumptions listed are referring to the EAG assumptions in the EAG model. The text should therefore be amended to improve clarity.	Amended for clarity.

Issue 7 EAG deterministic scenario analyses OS HR values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Executive Summary, Table 1, and Page 20, Executive Summary, Issue 3 The EAG note that "The EAG investigated a range of alternative HRs to the ITC value ([redacted]) so as to gauge the impact of HR for OS upon the company's economic analysis results.".	Please amend the text on Page 14, Executive Summary, Table 1 and Page 20, Executive Summary, Issue 3 as follows: "The EAG investigated a range of alternative HRs **(that used arbitrary values not based on data)** to the ITC value ([redacted]) so as to gauge the impact of HR for OS upon the company's economic analysis results.". J&J IM request that the following footnote is added to Table 5 and Table 49:	It should be made clear that the proposed OS HRs are arbitrary; they are not based on data and are instead presented to explore the impact of the HR on the ICER. This update will avoid misleading the reader.	Point of disagreement not factual inaccuracy.

Page 27, Executive Summary, Table 5 and Page 173, Section 5.1, Table 49 The EAG include scenario analyses in Table 5 and Table 49 using OS HRs for the comparison of talquetamab and teclistamab ranging from 0.55–0.90 in 0.05 increments in scenarios 2–9. Page 28–29, Executive Summary, Table 6 and Page 185–186, Section 5.5, Table 54 The EAG include scenario analyses in Table 6 and Table 54 using OS HRs for the comparison of talquetamab and teclistamab ranging from 0.55–0.90 in 0.05 increments in scenarios 7–14.	"[a]The OS HRs in scenarios 2–9 used arbitrary values that are not based on data and are solely used to explore the impact of this input on the ICER.". J&J IM request that the following footnote is added to Table 6 and Table 54: "[a] The proposed OS HRs in scenarios 7–14 used arbitrary values that are not based on data and are solely used to explore the impact of this input on the ICER.".		

Issue 8 Incorrect definition of RRMM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30, Section 1.1.1. The EAG note that "In the UK, the treatment options are	The statement should be updated as follows, in alignment with the CS: "In the UK, the treatment options are limited for patients **who have received previously**	The current definition of patients with TCE RRMM is incorrect. This should be updated to ensure accuracy of the	Corrected.

limited for patients categorised as RRMM i.e., patients who have had three previous lines of therapies also known as patients who are Triple Class Exposed (TCE)".	**exposed to an IMiD, a PI, and an anti-CD38 mAb and who have progressed on their last therapy** ~~categorised as RRMM i.e., patients who have had three previous lines of therapies also known as patients who are~~ **(referred to as** Triple Class Exposed (TCE)**.**".	submission population of interest. As outlined in Section 1.3 of the CS, RRMM patients are not equivalent to TCE and therefore it is inaccurate to imply this.	

Issue 9 Additional wording required to contextualise poor survival outcomes in TCE RRMM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31, Section 1.1.2 The EAG report the 5-year and 10-year survival rates for patients in England with myeloma, quoting "The 5-year and 10-year survival rates for patients in England with myeloma are 55% and 30%, respectively".	Please amend the text as follows: "The 5-year and 10-year survival rates for patients in England with myeloma **at all treatment lines** are 55% and 30%, respectively. **Patients with triple-class exposed (TCE) relapsed/refractory MM (RRMM) however are associated with much poorer survival, currently estimated to be slightly less than 2 years.**" The source for the survival estimate for TCE RRMM is based on the MajesTEC-1 trial which informed the NICE teclistamab appraisal (TA1015).[7]	These values referenced by the EAG are survival rates for all patients with newly diagnosed multiple myeloma. Therefore, these do not accurately reflect survival for patients with TCE RRMM which is the patient population of interest in this submission. TCE RRMM patients have a worse prognosis than non-TCE RRMM patients, with clinical experts consulted by the company estimating that their 10-year survival rate, based on currently available treatments, would be 10%. Following the introduction of teclistamab as a fourth-line and beyond (4L+)	Amended for clarity "at all treatment lines" added to page 32

		treatment option for patients with TCE RRMM, the median OS, based on the trial data is anticipated to be 22.2 months.[7] This section of the report should be updated to clarify that the quoted survival rates correspond to that of newly diagnosed MM patients rather than patients with TCE RRMM.	

Issue 10 Generalisability of MonumenTAL-1 to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 33, Section 1.2, Table 7 The EAG commented on generalisability issues of MonumenTAL-1 to UK clinical practice. The EAG noted that "It is unclear if the clinical evidence submitted by the company reflects the characteristics of the patient population in England and Wales eligible for treatment. Key trial evidence submitted for talquetamab contained no UK patients."	Page 33, Section 1.2, Table 7 Please amend the text as follows: "**The EAG note that the key trial evidence submitted for talquetamab contained no UK patients.** ~~It is unclear if t~~**The** clinical evidence submitted by the company **was however validated by UK clinical experts consulted by the company as part of the ingoing submission wherein the experts noted that the characteristics of the MonumenTAL-1 trial population were broadly generalisable to the target patient population in England and Wales.** ~~reflects the characteristics of the~~	It is important to highlight the UK clinical experts consulted as part of the ingoing submission concluded that the MonumenTAL-1 trial population was broadly representative of the target TCE RRMM population in UK clinical practice. The generalisability of MonumenTAL-1 to UK clinical practice was extensively discussed in Section 2.3.3 of the CS. This should, therefore, be reflected accordingly in the EAG critique; it is inaccurate to state that the trial is not	Not a factual inaccuracy. No change made.

A similar comment is provided on page 42, Section 2.1.3.1.1 The EAG noted that "The lack of UK patients limits the applicability of the results in terms of representativeness and generalisability for the UK context given differences in healthcare systems and practices especially including subsequent treatments in the 47 recruiting centres."	~~patient population in England and Wales eligible for treatment. Key trial evidence submitted for talquetamab contained no UK patients.~~" Page 42, Section 2.1.3.1.1 Please amend the text as follows: "The lack of UK patients limits the applicability of the results in terms of representativeness and generalisability for the UK context given differences in healthcare systems and practices especially including subsequent treatments in the 47 recruiting centres. **The EAG however acknowledge that the company applied subsequent treatment adjustment to ensure that OS data from MonumenTAL-1 informing the ITCs and economic model were only informed by UK-based subsequent treatment. It is also acknowledged that despite the lack of UK patients in the MonumenTAL-1 trial, the generalisability of the trial to UK clinical practice was validated by UK clinical experts consulted by the company.**".	generalisable to UK clinical practice without providing this additional context. Additionally, on Page 55 (Section 2.2.1.3) of the EAG report, the EAG note that "*the populations in both the MonumenTAL-1 and MajesTEC-1 trials included were broadly representative of the target population of TCE RRMM patients seen in routine UK practice as described in the NICE Final Scope*", thus contradicting the statement on Page 33 (Section 1.2) and Page 42 (Section 2.1.3.1.1). Furthermore, it is inaccurate to discuss the subsequent treatments in MonumenTAL-1 without also discussing the subsequent treatment adjustment that was performed. This is important to present a balanced argument which clearly highlights the inclusion of non-UK based subsequent treatments in MonumenTAL-1 did not ultimately impact the generalisability of the survival outcomes from MonumenTAL-1	

		in the ITCs and economic model.	
Page 43, Section 2.1.3.1 The EAG commented on the prior lines of therapy in Cohort C of MonumenTAL-1, as follows: "However, it is worth noting that the prior lines of therapy in Cohort C ranged from [redacted], with a median of 4.5. EAG clinical advisors suggest that the increased number of prior therapies received by patients in MonumenTAL-1 may not fully reflect the complex NHS treatment landscape for MM (see Figure 1)."	Please amend the text as follows: "However, it is worth noting that the prior lines of therapy in Cohort C ranged from [redacted], with a median of 4.5. **This implies that patients in MonumenTAL-1 are likely to have, on average, a higher number of prior lines of therapy, compared to UK clinical practice.** EAG clinical advisors suggest that the increased number of prior therapies received by patients in MonumenTAL-1 may not fully reflect the **number of prior lines of therapy received by TCE RRMM patients in UK clinical practice. Given that, as noted in Section 2.3.3 of the Company submission, studies have shown that increasing number of prior lines of therapy is associated with worse prognosis and response to treatment, the efficacy data observed in MonumenTAL-1 may represent a conservative underestimate of the "true" efficacy of talquetamab in less heavily pre-treated TCE RRMM patients seen in UK clinical practice.**[19, 20] ~~complex NHS treatment landscape for MM (see Figure 1)~~"	The current wording in the EAG report is unclear as to how the number of prior therapies received by patients in Cohort C of MonumenTAL-1 may not reflect the NHS treatment landscape. The wording in the report should therefore be updated to make explicit that the potential generalisability issue is that patients in MonumenTAL-1 may be more heavily pre-treated vs patients in UK clinical practice. Additionally, the potential impact on results should be clearly stated to aid interpretation of this potential generalisability concern raised by the EAG. The data provided in the EAG report implies that, on average, patients in MonumenTAL-1 were more heavily pre-treated vs the anticipated target patient population in UK clinical practice (i.e., 4L+ TCE RRMM).	Not a factual inaccuracy. No change made.

		As highlighted in Section 2.3.3 of the CS, “Increasing lines of prior therapy is known to be associated with a worsened symptom burden, prognosis and response to treatment, the efficacy data observed in the MonumenTAL-1 trial is therefore highly likely to represent a conservative underestimate of the ‘true’ efficacy of talquetamab in less pretreated TCE RRMM patients seen within UK NHS cancer services.[19, 20]” The wording in the EAG report should therefore be updated to more accurately reflect the EAG’s generalisability concern and the potential impact this may have, if any, on the generalisability of the trial results.	

Issue 11 Clarification of the provision of patient reported outcome (PRO) data from MonumenTAL-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37, Section 1.2, Table 7 The EAG noted that "patient reported outcomes (PRO) were not included in the clinical evidence provided in the CS". Page 49, Section 2.1.4, Table 10 The EAG stated "The company noted that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline and therefore not presented. It will be provided as an addendum when possible."	Please amend the text as follows: Page 37, Section 1.2, Table 7 "Patient reported outcomes (PRO) were not **initially** included in the clinical evidence provided in the CS but **were provided as an addendum accompanying the clarification question response.**". Page 49, Section 2.1.4, Table 10 Please amend the text as follows: "The company noted that the write-up of PRO data from the September 2024 DCO was not available in time for the submission deadline, ~~and therefore not presented. It will be provided as an addendum when possible.~~ **These were instead provided as an addendum alongside the company clarification question response**.".	PRO outcome data from MonumenTAL-1 were provided as an addendum alongside the Company's clarification question response. These statements should be updated to provide clarity that these data have been provided by the Company.	Amended where requested.

Issue 12 Additional wording required to clarify the MonumenTAL-1 inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42, Section 2.1.3.1.1 The EAG noted that "The subcutaneous (SC) doses of 0·4 mg/kg once a week and 0·8 mg/kg every two weeks were identified in phase I and were evaluated in phase II in patients who were 18 years of age or older, had at least three previous lines of therapy, had an Eastern Cooperative Oncology Group performance status of 0 to 2, and were naive or exposed to previous T-cell redirection therapy (TCR)."	Please amend the text as follows: "The subcutaneous (SC) doses of 0·4 mg/kg once a week and 0·8 mg/kg every two weeks were identified in phase I and were evaluated in phase II in patients who were 18 years of age or older, had at least three previous lines of therapy **including at least one IMiD, one PI, and an anti-CD38 mAb (TCE)**, had an Eastern Cooperative Oncology Group performance status of 0 to 2, and were naive or exposed to previous T-cell redirection therapy (TCR)"	The current text does not mention that the patients enrolled in MonumenTAL-1 need to be triple-class exposed. Update to clarify patients in the MonumenTAL-1 trial are TCE RRMM.	Amended.

Issue 13 Inaccurate presentation of the MajesTEC-1 patient cohorts

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Section 2.2.1.2, Table 13 The EAG have incorrectly presented the dose for the	Please amend the table as follows:	The EAG have incorrectly presented the dose for the MajesTEC-1 study patient Cohorts B and C; these should therefore be updated to	Corrected.

MajesTEC-1 study patient Cohorts B and C.	**Table 1: MajesTEC-1 study patient cohorts.** **Patient cohort, prior TCR exposure** / **Dose of teclistamab** / **Phase, part # (sample size)** **RP2PD sample - No prior TCR exposure (patients with RRMM TCE)** / **RP2PD 1.5 mg/kg weekly SC** / **Phase I, part 2 (n=40)** **Cohort A - No prior TCR exposure (patients with RRMM TCE)** / **RP2PD 1.5 mg/kg weekly SC** / **Phase II, part 3 (n=125)** Cohort B - No Prior TCR exposure / ~~0.4 mg/kg weekly SC or 0.8 mg/kg~~ / Phase II, part 3 (n=0)	accurately reflect the MajesTEC-1 patient cohorts dosing.	

	Heavily pre-treated patients considered penta-drug refractory	~~every two weeks SC~~ **RP2PD 1.5 mg/kg weekly SC**			
	Cohort C - Prior TCR exposure	~~0.8 mg/kg every two weeks SC~~ **RP2PD 1.5 mg/kg weekly SC**	Phase II, part 3 (n=40)		
	RP2PD=recommended phase-2 dose; T-cell receptor therapy; RRMM=relapsed and refractory multiple myeloma; Q2W=biweekly; QW=weekly; SC=subcutaneous **BOLD: Cohorts included in the ITC**				

Issue 14 Incorrect description of the adverse event (AE) comparison between MonumenTAL-1 and MajesTEC-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 61, Section 2.2.2.1.3 The EAG note that "The company's ITC analysis included the incidence of the following safety outcomes compared between the talquetamab (MonumenTAL-1)	J&J IM request that the EAG move subsection 2.2.2.1.3 and Section 2.2.6 of the EAG report to their own sections of the EAG report. The title of this section should read: "~~ITC Results:~~ **Naïve comparison of the**	The inclusion of the safety comparisons provided in Section 2.11 of the CS in Section 2.2 of the EAG report is inaccurate as it implies that formal analyses, including adjusting for the prognostic	Amended to naïve comparison.

and teclistamab (MajesTEC-1) arms:" Page 83, Section 2.2.6 The EAG title for this section is "ITC Results: adverse reactions" Page 87, Section 2.2.6.1.1 The EAG state that "The ITC results indicate that talquetamab demonstrated comparable (for CRS, AEs of Metabolic/Nutrition disorders System Organ Class/SOC) or a better safety (for total grade 3-4 TEAEs, AEs of Blood/Lymphatic System Disorders SOC, any grade infections, grade 3/4 infections, fatal infections) profile compared to teclistamab".	**adverse reactions in MonumenTAL-1 and MajesTEC-1**". In this new section, the EAG should note the following: "**In Section 2.11 of the CS, t**~~T~~he ~~company's ITC analysis included~~ company performed naïve comparisons of the incidence of the following safety outcomes compared between the talquetamab (MonumenTAL-1) and teclistamab (MajesTEC-1) arms:" "**In these naïve comparisons,** talquetamab demonstrated comparable (for CRS, AEs of Metabolic/Nutrition disorders System Organ Class/SOC) or a better safety (for total grade 3-4 TEAEs, AEs of Blood/Lymphatic System Disorders SOC, any grade infections, grade 3/4 infections, fatal infections) profile compared to teclistamab."	factors outlined in Section 2.2.2 of the EAG report, were conducted on the respective safety data for talquetamab and teclistamab from the MonumenTAL-1 and MajesTEC-1 trials, when the comparisons were naïve in nature. To improve accuracy, the naïve comparisons on safety data between trials should be moved to its own section of the EAG report. Additionally, all mentions of ITCs relating to this comparison should be removed.	

Issue 15 Incorrect description of the results of the two-stage subsequent treatment adjustment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54, Section 2.2.2.5 The EAG incorrectly state that "The model estimated the treatment effect, i.e., an	Please amend the text as follows: "The model estimated the treatment effect, i.e., an acceleration factor (AF) associated with switching to subsequent treatments	As noted on Page 99 (Section 2.10.4) of the CS, "Using [the two-stage adjustment method], the survival time was reduced	Amended.

acceleration factor (AF) associated with switching to subsequent treatments not routinely used in the UK. The company noted that the switching to treatments not routinely used in the UK was associated with reduced survival times compared to switching to treatments routinely available in the UK.”.	not routinely used in the UK. The company noted that the switching to treatments not routinely used in the UK was associated with **longer** ~~reduced~~ survival time~~s~~ compared to switching to treatments routinely available in the UK.”.	for patients initiating a subsequent treatment which is not available in routine UK clinical practice.”, the opposite of what the EAG state in their report. The existing statement is therefore factually inaccurate and should be updated accordingly.	

Issue 16 Clarification on interpretation of multivariable regression analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, Section 2.2.3 The EAG note that “The results indicated that patients with extramedullary disease (EMD), higher ISS stages, or male gender had a [redacted] ORR. In particular, the presence of EMD, a higher number of prior lines, lower haemoglobin, and non-IgG MM type were found to be associated with [redacted] PFS and OS outcomes.”. The sub header of Table 16 states “[Outcome] point	Please amend the text as follows: “The results indicated that patients with extramedullary disease (EMD), higher ISS stages, or male gender had a [redacted] ORR **relative to baseline**. In particular, the presence of EMD, a higher number of prior lines, lower haemoglobin, and non-IgG MM type were found to be associated with [redacted] PFS and OS outcomes **relative to baseline**.”. Please amend the text in the Table 16 sub header as follows:	Table 16 presents the results of the multivariable regression analyses for all baseline prognostic factors. The right-hand column of the table states that the point estimates are based on talquetamab versus teclistamab comparison. This is not correct. The point estimates are reflective of the prognostic value of the particular covariate relative to baseline – they do not represent comparisons of talquetamab with teclistamab. As such the description of the	Amended for clarity.

estimate (95% CI) (talquetamab vs. teclistamab)"	"[Outcome] point estimate (95% CI) **relative to baseline for** ~~(~~talquetamab **and**~~vs.~~ teclistamab~~)~~"	point estimate should be updated in both Table 16 and the associated text to accurately reflect the outcome of the multivariable regression analyses.	

Issue 17 Textual amendment or additional wording required in EAG critique of Company ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93, Section 2.3 The EAG commented that "Although the prognostic value assessment performed for CARTITUDE-1 remains relevant to the 4L+ TCE RRMM patients in MonumenTAL-1 trial, the same validation of the MonumenTAL-1 IPD might have generated a different set of unmeasured important covariates associated with the RRMM prognosis outcomes."	Please amend the text as follows: "~~Although t~~**T**he prognostic value assessment performed for CARTITUDE-1 **was validated by clinical experts in TA1015, therefore confirming that these prognostic variables remain relevant to the 4L+ TCE RRMM patient population of interest.** ~~remains relevant to the 4L+ TCE RRMM patients in MonumenTAL-1 trial, the same validation of the MonumenTAL-1 IPD might have generated a different set of unmeasured important covariates associated with the RRMM prognosis outcomes~~.".	The list of covariates associated with RRMM prognosis had been re-validated by UK clinical experts consulted as part of TA1015, thereby confirming that these prognostic variables remain relevant to the 4L+ TCE RRMM patient population of interest. The EAG did not acknowledge that the prognostic variables have been re-validated as part of TA1015. Additionally, as noted on Page 62 of the EAG report (Section 2.2.2.2), clinical advisors to the EAG "*confirmed the covariates selected were appropriate for this population*.", further reflecting the relevance of the covariates in this setting.	No change made. Not a factual inaccuracy.

		It is therefore not factually accurate to imply that it is unknown whether covariates are relevant in this setting; this statement should therefore be updated.	

Issue 18 Textual amendment or additional wording required in EAG critique of the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 99, Section 3.3.1, Table 25, Comparator(s) row The EAG commented on the company's submission as follows: "Several comparators included in the NICE scope, but company has only compared talquetamab versus teclistamab"	Please amend the text as follows: "Several comparators included in the NICE scope, but company ~~has~~ only compared talquetamab versus teclistamab**; EAG clinical advisors confirmed that teclistamab is the most relevant comparator for this appraisal and the EAG accept teclistamab as the most relevant comparator for this appraisal**."	The current wording omits the agreement from both EAG clinical advisors and clinical experts consulted by J&J IM who agreed that teclistamab represented the most relevant comparator to talquetamab. The current text in the table is unclear on whether this approach is appropriate. Given that the EAG and EAG clinical advisors concluded that the comparator selection was appropriate this should be clarified within the table to aid interpretation.	Removed "has".

Issue 19 Clarification of the characteristics and dosing regimen of MonumenTAL-1 Cohort C

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108, Section 3.4.6 There is a typographical error and lack of clarity in the sentence: "The talquetamab population was termed Cohort C; it was winnowed from the MonumenTAL-1 study population to represent a Triple Class Resistant (TCR) group that had progressed after three previous interventions and who received a company-selected talquetamab dose regimen."	Please amend the text as follows: "The talquetamab population was termed Cohort C; ~~it was winnowed from~~ **this referred to** the MonumenTAL-1 study population **consisting of patients who had TCE RRMM, who had not received prior T-cell redirecting therapy and** ~~to represent a Triple Class Resistant (TCR) group that~~ had progressed after three previous interventions and who received **the recommended phase 2 dose (RP2D) of 0.8mg/kg SC every two weeks**~~a company-selected talquetamab dose regimen~~.".	The MonumenTAL-1 trial patient population consisted of triple-class exposed (TCE) RRMM patients – this is different from triple-class resistant. Moreover, it should be clarified that the company-selected talquetamab dose regimen is in line with the recommended phase 2 dose. This section needs updating to accurately reflect the patient characteristics of Cohort C.	Amended for clarity.

Issue 20 Clarification of the OS ITC results before and after subsequent treatment adjustment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 108, Section 3.4.6 The EAG state "After **the ITC** adjustments deemed reasonable on clinical advice,	Please amend the text as follows: "After **the ATT-**adjustments deemed reasonable on clinical advice, the hazard ratio, **before subsequent treatment**	This statement requires additional clarification to explain that these values are before and	Amended for clarity.

the hazard ratio became [redacted]), a value similar to the indirect treatment comparison (ITC) value of [redacted]applied by the company to the company's teclistamab OS lognormal model to aid development of the company's base-case talquetamab OS lognormal model."	**adjustment,** became [redacted]), a value similar to the indirect treatment comparison (ITC) value **after the base case subsequent treatment adjustment of** [redacted]applied by the company to the company's teclistamab OS lognormal model to aid development of the company's base-case talquetamab OS lognormal model.".	after subsequent treatment adjustment.	
Page 118, Section 3.4.7 The EAG state that "Although PFS is [redacted] between arms (ITC HR = [redacted]), talquetamab OS is [redacted] to teclistamab OS (reported unadjusted HR = [redacted], adjusted HR = [redacted] and ITC HR =[redacted]).".	Please amend the text as follows: "Although PFS is [redacted] between arms (ITC HR = [redacted]), talquetamab OS is [redacted] to teclistamab OS (reported unadjusted HR = [redacted], **ATT** adjusted **(main ITC)** HR = [redacted] and **base case subsequent treatment adjusted** ITC HR =[redacted])."	It is not clear which ITC analysis each of the OS HRs are referring to. Update to improve clarity.	Amended.

Issue 21 Clarification of the exclusion of subsequent talquetamab in the company base-case economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 175, Section 5.1, Table 50 In the subsequent talquetamab treatment row the table states that the company "Excluded	Please amend the text as follows: "Excluded subsequent talquetamab in the teclistamab arm**, which is reflective of current UK clinical practice**."	J&J IM request that additional context explaining that the subsequent treatment adjustment was performed to align with UK clinical practice is added to this statement for clarity and to aid interpretation of the	Amended.

subsequent talquetamab in the teclistamab arm.”.		appropriateness of this approach.	

Issue 22 Incorrect assumption of double counting of AE disutilities

Page 175, Section 5,1 and Page 177, Section 5.3 The EAG state that “The EAG consider that the inclusion disutilities associated with adverse events may result in double counting.”.	J&J IM request that the EAG remove these statements from the report, as well as the associated scenario analysis reported in row 16 of Table 51 (Page 176, Section 5.1)	Given the extended intervals between each PRO assessment (as detailed in the company’s PRO summary addendum, “PRO data were collected at screening and then at day 1 of every 28-day cycle until the end of treatment”), as well as the transient nature of the AEs, it is unlikely that the impact of these AEs of patients’ HRQoL is fully captured within the health state utility values. As such, it is factually inaccurate to state that their inclusion results in double counting and the EAG report should be updated to reflect this.	**EAG response** Point of disagreement not factual inaccuracy, no change made.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22, Executive Summary, Issue 5 There is a typographical error in the sentence: “At cut-off (after about 40 months) 71% of Cohort C have had an infection while at 36 months 61% are still alive and can receive IVIg. In contrast at MajesTIC-1 cut off [redacted]% have had an infection but only [redacted]% are still alive to receive IVIg.” Page 102, Section 3.4.5 There is a typographical error in the sentence: “While it is true that the survival analysis methodology was previously used in TA1015, the relevance of the underlying survival data from the MajestTEC-1, which informed the survival model for	Correct the spelling of “MajesTIC-1” and “MajestTEC-1” to **MajesTEC-1.**	Update the spelling of the typographical error to ensure correct spelling.	Amended

teclistamab, is questionable due to the substantial rate of COVID-related deaths observed in the trial (see Section 2.2.7).".			
Page 15, Executive Summary Table 1 and Page 23, Executive Summary, Issue 6 The EAG have incorrectly said that the "Inclusion of the subsequent talquetamab treatment increased the company's base-case ICER by [redacted]%."	Please amend the text in both instances as follows: "Inclusion of the subsequent talquetamab treatment reduced the company's base-case ICER by -[redacted]%".	Update to ensure the impact to the company's base case ICER in the Executive Summary are accurately presented as per Table 2 of the Executive Summary.	Amended
Page 24, Executive Summary, Summary of EAG's preferred assumptions and resulting ICER and Page 177, Section 5.3 The EAG incorrectly present their preferred assumptions for generating long-term estimates for teclistamab as:	Please amend the text in both sections as follows: • **Unc**~~C~~alibrated Weibull modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS. • **Unc**~~C~~alibrated Weibull modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS. • **Unc**~~C~~alibrated Weibull modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD.	The EAG used the uncalibrated Weibull so the statements need updating to reflect the correct curve selected by the EAG.	Amended

• Calibrated Weibull modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS. • Calibrated Weibull modelling of teclistamab PFS, then applying the ITC PFS HR ([redacted]) to generate talquetamab PFS. • Calibrated Weibull modelling of teclistamab TTD, then applying the ITC TTD HR ([redacted]) to generate talquetamab TTD.			
Page 26, Executive Summary, Table 4 The EAG note in the text and caption of Table 4 that the "EAG deterministic base-case results" are presented, under the subheading	Please amend the text as follows: "In Table 4, we present the EAG ~~deterministic~~ **probabilistic** results based on the EAG's preferred assumptions. The caption for Table 4 should read "Table 4: EAG's ~~deterministic~~ **probabilistic** base-case results, using PAS prices".	Given the EAG deterministic results are already presented in Table 3 before this, J&J IM believe there to be a typographical error in the caption and text accompanying Table 4.	Amended

"EAG probabilistic sensitivity analysis results".		Update to ensure the results are accurately presented.	
Page 31, Section 1.1.2 The EAG note that "Globally, MM accounts for approximately 2% of all new cancer cases (estimated in 2016-2018)."	Please amend the text as follows: "Globally, MM accounts for approximately 2% of all new cancer cases (estimated in ~~2016-2018~~**2017–2019**)."	As noted in Section 1.3.2 of the CS, this statistic was based on data collected between 2017–2019 according to Cancer Research UK. The dates should therefore be updated to accurately capture when the statistic was measured.	Amended
Page 31, Section 1.1.2 The EAG incorrectly reference the NICE appraisal of Daratumumab as [TA738]	Correct [TA738] to [**TA783**]	TA738 is the incorrect appraisal; it is the appraisal for berotralstat for preventing recurrent attacks of hereditary angioedema. The appraisal for daratumumab should therefore be updated to the correct technology appraisal.	Amended
Page 37, Section 1.2, Table 7 The EAG commented that "The outcomes are largely similar with the addition of	Please amend the text as follows: "The outcomes are largely similar with the addition of Minimal residual disease (MRD)-**negativity rate**."	Update to accurately reflect the trial outcome included.	Amended

Minimal residual disease (MRD).”			
Page 39, Section 2.1.1 The EAG note that “The electronic database search strategies reported in CS tables 1-8”.	Please amend the text as follows: ““The electronic database search strategies reported in the CS **Appendix** tables 1-8”.	These tables are provided in the CS appendix, rather than the main evidence submission. Update to ensure the correct document is referred to.	Amended
Page 41, Section 2.1.2.1 The EAG incorrectly say that “The original SLR included 456 publications reporting on 218 unique studies”.	Correct the value of “456” to “**455”**.	In the CS Appendix B.1.3, Page 60, J&J IM state that “In total, 455 publications reporting on 218 unique studies met the inclusion criteria.”. Update to ensure the number of publications is accurate.	Amended
Page 41, Section 2.1.2.1.1 The EAG say that “In total, 121 publications reporting on 23 unique studies on talquetamab or teclistamab were selected”, and later in that paragraph that “The company did not provide detailed study	Correct the value of “121” to “**122”** in both instances.	In CS Appendix B.1.3, Page 62, J&J IM state that “In total, 122 publications reporting on 23 unique studies on talquetamab or teclistamab were selected for extraction for the purposes of this submission.”.	Amended

characteristics for all the 121 publications in the original CS".		Update to ensure the correct number of publications are referred to.	
Page 41, Section 2.1.2.1.1 The EAG state: "The number of participants randomised or enrolled in 23 studies ranged from [redacted] (see CS Appendix Table 13).".	Correct "CS Appendix Table 13" to "CS Appendix Table **15**".	This information is provided in Table 15 of the CS Appendix.	Amended
Page 41, Section 2.1.2.1.1 The EAG have incorrectly noted that "none of these 23 studies included a UK population".	Please amend the text as follows: "The EAG note that none of these 23 studies included **a population solely consisting of UK**."	Whilst it is true that none of the studies included a population consisting only of patients from UK clinical practice, it is not true to say that none of the studies included a UK population. As highlighted in Issue 4, the MajesTEC-1 trial which was included in the 23 studies included 9 patients from the UK. Update to ensure the statement is factually accurate and not misleading.	Amended
Page 49, Section 2.1.4	Please amend the text as follows:	These data are reported on Page 53 of the CS.	Amended

The EAG note that the "Baseline characteristics of these patients were reported in CS Section 2.3.3 (CS Table 7; Page 57).".	"Baseline characteristics of these patients were reported in CS Section 2.3.3 (CS Table 7; **Page 53**).".	The page number should therefore be updated to ensure the correct page is linked to in the report.	
Page 50, Section 2.1.5.1 The EAG note that "Cohort B included more heavily pre-treated patients who had experienced more than five lines of treatment and was not open for enrolment".	Please amend the text as follows: "Cohort B included more heavily pre-treated patients who had experienced **at least 4** lines of treatment and was not open for enrolment.".	Cohort B of the MajesTEC-1 trial included patients who had experienced at least four lines previous therapy, as per Figure 8 (Section 2.3.1) of the CS for teclistamab in TA1015.[7] This statement should therefore be updated to ensure the characteristics of Cohort B in MajesTEC-1 are correctly reported.	Amended
Page 60, Section 2.2.2 The EAG incorrectly state that [redacted]% of the sturdy participants did not complete the MonumenTAL-1.	Correct the value of [redacted]% to [redacted]**%**.	The correct value is [redacted]% as per Page 56, Section 2.4.1 of the CS.	Amended
Page 62, Section 2.2.2.3 The EAG state that "The company calculated SMDs indicating the between-arm mean	Correct "SMD>0.2" to "SMD > **+/-** 0.2".	An SMD > +/- 0.2 was suggestive of imbalance, as per Section 2.10.3 of the CS."	Amended

difference for each covariate, with an SMD > 0.2 suggesting a substantial difference (i.e., imbalance)."			
Page 64, Section 2.2.2.5 There is a typographical error in the sentence "Whilst this approach is in line with the approach accepted by NICE in the appraisal for teclistamab (TA1015)[6], the EAG clinical advisors highlight the large variation is subsequent treatments outside and within UK clinical care."	Please amend the text as follows: "Whilst this approach is in line with the approach accepted by NICE in the appraisal for teclistamab (TA1015)[6], the EAG clinical advisors highlight the large variation **is~~s~~n** subsequent treatments outside and within UK clinical care."	Update to ensure the statement reads correctly.	Amended
Page 65, Section 2.2.2.5.1 There is a typographical error in the bullet point "All-out (scenario 1) and All-in (scenario 2). In the base case scenario".	Please amend the text as follows: "~~All-out (scenario 1) and All-in (scenario 2). In the~~ **B**ase case scenario".	The content corresponds to the Company base case rather than the scenarios and therefore the bullet should be updated to improve clarity.	Amended
Page 66, Section 2.2.3, Table 16 There is a data error in the row "Number of prior	Please amend the text as follows: "SS [PFS] HR=[redacted] ([redacted])".	Update to ensure the data are correctly reported in line with Figure 10 in CS	Amended

LOTs (4+ vs. ≤4)", the 95% CI for the statistically significant (SS) PFS HR incorrectly reads "([redacted])".		Appendix B.1.6 (Page 111).	
Page 73, Section 2.2.5.1.1 The EAG state that "For MonumenTAL-1 Cohort C, no data imputation was performed and a separate category "Missing" was created to describe the proportion of missing values ([redacted]% lost to follow-up).".	Correct the value from [redacted]% to [redacted]%.	Update to ensure the proportion of patients quoted in MonumenTAL-1 Cohort C lost to follow-up is in line with that reported in the CS (Section 2.4.1, Table 9).	Amended
Page 73, Section 2.2.5.1.1 The EAG state that "The proportion of missing data for cytogenetic profile was about [redacted]% however, no imputation was performed for these data and instead, 'missing' was added as a categorical variable.".	Correct the value from [redacted]% to [redacted]%.	The CS Appendix B.1.6 (Page 107) shows that this value to one decimal place is [redacted]%, and as such this value should be rounded to [redacted]%. Update to ensure the correct value is reported.	Amended
Page 76, Section 2.2.5.1.3	Please amend the text as follows:	The correct 95% CI is not estimable, not estimable.	Amended

<table>
<tr>
<td>There is a missing value and typographical error in the statement “The OS KM curves presented in Figure 7 indicate that patients receiving talquetamab experienced [redacted] median time to death (not estimable, 95% not estimable)”.</td>
<td>“The OS KM curves presented in Figure 7 indicate that patients receiving talquetamab experienced [redacted] median time to death (not estimable, 95% CI: not estimable, not estimable)”.</td>
<td>Update to ensure the results are correctly presented</td>
<td></td>
</tr>
<tr>
<td>Page 80, Section 2.2.5.1.5, Table 21

Compared to Table 26 of the CS (Section 2.10.4), Table 21 of the EAG report is missing three of the non-UK relevant subsequent treatments received by patients in MajesTEC-1. These are:

Elotuzumab ([redacted])

Etoposide ([redacted])

Melfufen ([redacted])</td>
<td>Please add the following rows to Table 21:
<table>
<tr><th rowspan="2">Patients receiving subsequent therapy (%)</th><th colspan="2">Before subsequent treatment adjustment</th><th colspan="2">After adjustment (re-weighting) for subsequent treatment (Base case scenario)</th></tr>
<tr><th>Talquetamab (MonumenTAL-1; Cohort C) N=[redacted][a]</th><th>Teclistamab (MajesTEC-1) N=[redacted][b]</th><th>Talquetamab (MonumenTAL-1; Cohort C)[c]</th><th>Teclistamab (MajesTEC-1)[c]</th></tr>
<tr><td colspan="5">Non-UK relevant subsequent treatments</td></tr>
<tr><td>Elotuzumab</td><td>-</td><td>[redacted]</td><td></td></tr>
<tr><td>Etoposide</td><td>-</td><td>[redacted]</td><td></td></tr>
<tr><td>Melfufen</td><td>-</td><td>[redacted]</td><td></td></tr>
</table></td>
<td>Update to ensure the full list of non-UK relevant subsequent treatments received by patients in MajesTEC-1 is presented.</td>
<td>Amended</td>
</tr>
<tr>
<td>Page 83, Section 2.2.6

The EAG state that “The proportion of patients with at least one Grade 3/4 TEAE was [redacted] in MajesTEC-1 (teclistamab)</td>
<td>Please amend the text as follows:

“The proportion of patients with at least one Grade ≥3~~/4~~ TEAE was [redacted] in MajesTEC-1 (teclistamab) versus MonumenTAL-1 (talquetamab) ([redacted]% vs. [redacted]%),”.</td>
<td>These values, as calculated from Table 39 (Section 2.11.2) of the CS for talquetamab and Table 30 (Section 2.10.2) of the teclistamab CS</td>
<td>Amended</td>
</tr>
</table>

versus MonumenTAL-1 (talquetamab) ([redacted]% vs. [redacted]%),”.		represent the proportion of patients with at least one ≥3 Grade 3 TEAE, and encompass patients with Grade 5 TEAEs. Additionally, according to Table 30 of the teclistamab CS, the proportion of patients with at least one ≥3 Grade 3 TEAE is [redacted]%. Update to ensure the results are correctly presented.	
Page 83, Section 2.2.6 There is a typographical error in the statement “Accordingly, the dose modification (delay, modification, skip) was more [redacted] in teclistamab compared to talquetamab ([redacted]% vs. [redacted]%).”.	Please amend the text as follows: “Accordingly, the dose modification (delay, **reduction** ~~modification~~, skip) was more [redacted] in teclistamab compared to talquetamab ([redacted]% vs. [redacted]%).”.	Footnote “[a]” of Table 39 in the CS (Section 2.11.2) states that “Dose modification includes delays within cycle, dose reduction and dose skipped.”.	Amended
Page 83, Section 2.2.6 The EAG names this section as “ITC Results: adverse reactions”.	Please amend the text as follows: “~~ITC results:~~ **Naïve comparison: A**~~a~~dverse reactions”	No ITCs were conducted for adverse reactions, the title of the section therefore requires updating to reflect this in	Amended

		order to improve clarity of the title.	
Page 86, Section 2.2.6 The statement “However, the company has not considered the substantial rate of patients who received IVIg in the MajesTEC-1, when compared to the NHS practice observed in the UK.” is missing the word “trial”.	Please amend the text as follows: “However, the company has not considered the substantial rate of patients who received IVIg in the MajesTEC-1 **trial**, when compared to the NHS practice observed in the UK.”.	Update to improve clarity.	Amended
Page 88, Section 2.2.7 The EAG note that there were “Potentially healthier patient populations in the trials (explored by the EAG in Section 3.3.6 EAG additional analysis and Table 17)”.	Please amend the text as follows: “Potentially healthier patient populations in the trials **compared to real-world evidence** (explored by the EAG in Section 3.3.6 EAG additional analysis and Table 17)”.	While J&J IM agree that the trial populations may potentially be healthier compared to real-world evidence, it is not true that the population in the MonumenTAL-1 trial is healthier than that of MajesTEC-1, as noted in Section 2.3.3 of the CS. Update to improve the clarity and accuracy of the statement.	Amended
Page 90, Section 2.2.7 When discussing the discontinuation rates due	J&J IM request that this factual inaccuracy is removed from the paragraph.	J&J IM do not agree that this is an overestimation as it was what the data from the trials is currently	Removed

to disease progression in MonumenTAL-1 and MajesTEC-1, the EAG state that “If this is the case, the supposed worsened prognosis of this ‘untreated’ patient group might have overestimated the OS benefit by certain magnitude in favor of the talquetamab arm.”.		showing, and as such, the only comparison that can be made.	
Page 94, Section 2.3 There is a typographical error in the sentence “The EAG has conducted additional analysis presented in Section 3.4.6 inform the EAG base case.”.	Please amend the text as follows: “The EAG has conducted additional analysis presented in Section 3.4.6 **to** inform the EAG base case.”.	Correct typographical error to improve clarity.	Amended
Page 97, Section 3.2.1 The text incorrectly states that “Searches for both SLRs were undertaken in June 2024”.	Please amend the text as follows: “The searches for both SLRs were undertaken in **December 2024**”	Month is currently incorrect and requires updating.	Amended
Page 99, Section 3.3.1, Table 25 The EAG incorrectly commented that “in the	Please amend the text as follows: “in the model, utilities were treatment-**in**dependent”	The description of the utilities used in the economic model is	Amended

model, utilities were treatment-dependent".		inaccurate and requires updating.	
Page 102, Section 3.4.2.1 The text currently states "a maintenance dose of 0.8**mb**/kg"	Please amend the text as follows: "a maintenance dose of 0.8**mg**/kg"	The unit is incorrect and should be updated to the correct unit.	Amended
Page 102, Section 3.4.2.1 The EAG incorrectly noted the dosing regimen for talquetamab, as follows: "In the base-case, in line with the RealiTAL real-world study, 88% and 12% of the participants began talquetamab on a dosing regimen of every two weeks and weekly, respectively. In scenario analysis, the company assumed that 90% and 12% of people began weekly and every two weeks treatment, respectively."	Please amend the text as follows: "In the base-case, ~~in line with the RealiTAL real-world study, 88% and 12% of the~~ **all** participants **received** ~~began~~ talquetamab on a dosing regimen of every two weeks ~~and weekly, respectively~~. In **a** scenario analysis, the company assumed that **10%**~~90%~~ and **90%**~~12%~~ of people began weekly and every two weeks treatment, respectively**, in line with UK clinical expert opinion**."	All patients in the base case analysis received talquetamab on a dosing regimen of every two weeks so the statement regarding the base case dosing regimens is inaccurate. The scenario analysis regimen stated is also inaccurate and should be updated in line with the CS, Page 188, Table 79. These proportions were based on UK clinical expert feedback received which were supported by the RealiTAL real-world study data, in which 88% of patients begun their talquetamab treatment on the biweekly dosing regimen.[21]	Amended

		Update to accurately reflect modelling approach taken for base case and scenario analyses.	
Page 102, Section 3.4.2.2 The EAG commented that "The approach taken by the company to model a reduced dose frequency of teclistamab is plausible although several additional comparators were included in the NICE scope for this appraisal."	J&J IM suggests the EAG to provide additional context to the statement made.	It is unclear why the inclusion of additional comparators is linked to the plausibility of reduced teclistamab dose frequency. The text should be updated to clarify why the inclusion of additional comparators in the NICE scope is linked to the plausibility of reduced teclistamab dose frequency, or alternatively, the latter part of the sentence (starting from 'although') should be removed altogether.	
Page 102, Section 3.4.5 There is a typographical error in the sentence: "In TA1015, the company fit parametric models (exponential, Weibull, log-	Correct the abbreviation of TNT to **TTNT.**	Update the spelling of the typographical error to ensure correct spelling.	Amended

normal, log-logistic, Gompertz, generalised gamma, and gamma) to the MajesTEC-1 IPD for OS and time-to-next treatment (TNT) as a proxy for PFS.".			
Page 107, Section 3.4.5 There is a typographical error in the sentence "recently publishes real world studies are consistent with the company's likely over-estimation of survival of talquetamab recipients and underestimation of survival of teclistamab recipients.".	Please amend the text as follows: "recently published~~s~~ real world studies are consistent with the company's likely over-estimation of survival of talquetamab recipients and underestimation of survival of teclistamab recipients.".	Update typographical error to ensure the correct word is used.	Amended
Page 107, Section 3.4.5 The EAG note that "Additionally, the choice to use a single model across OS, PFS, and TTD needs further justification, as these outcomes, while interlinked, frequently do not share identical hazard functions.".	Please amend the text as follows: "Additionally, the choice to use a single model across OS, PFS, and TTD needs further justification, as these outcomes, while interlinked, frequently do not share identical hazard functions. **J&J IM provided further justification to this effect in the company clarification question response, in answer to question B.1**."	J&J IM provided further justification to this point in response to clarification B.1 in the clarification questions response, which should be referenced here.	Amended

Page 107, Section 3.4.5 The EAG state that log-normal estimates from the TA-1015 submission are "**13**% survival at 10 years, and 9% at 15 years"	Correct the value of 13% to **14**%.	Value should be corrected as per Table 37 of the TA1015 committee papers	Amended
Page 108, Section 3.4.5.2, Table 29 The INHB for "Weibull individually fit on talquetamab" is incorrectly reported as 0.33.	Correct the value of 0.33 to **0.34**.	Value should be corrected as per Table 80 of the Company submission.	Amended
Page 122, Section 3.4.7.1 The text states that "[redacted] treatments were condensed into groups"	Correct the value of [redacted] to [redacted].	Value should be corrected as per Table 73 of the Company submission appendices.	Amended
Page 123, Section 3.4.7.1, Figure 25 The figure caption for the teclistamab OS and PFS curve incorrectly spells teclistamab as "tecistamab".	Please amend the text as follows: "Economic model **teclistamab** OS and PFS".	Caption should be updated to correct typographical error.	Amended
Page 127, Section 3.4.7.3 The text states that 95% CI for the ITC OS HR	Correct the range from "[redacted] to [redacted]" to "[redacted] to [redacted]"	Value should be corrected as per Table 32 of the company submission.	Amended

spanned the range [redacted] to [redacted]			
Page 129, Section 3.4.7.4 The text states that "The median TTD for teclistamab was approximately [redacted] months".	Please amend the text as follows: "The median TTD for teclistamab was approximately [redacted] months".	Value should be corrected as per the Company submission model.	Amended
Page 130, Section 3.4.7.4 The text states that "This was done by making the lognormal extrapolation conform to clinical advisor estimates of the proportion in treatment at ten years (**0.3**%) and fifteen years (**0.1**%).".	Please amend the text as follows: "This was done by making the lognormal extrapolation conform to clinical advisor estimates of the proportion in treatment at ten years (**3**%) and fifteen years (**1**%).	Values should be correct as per Table 55 of the Company submission.	Amended
Page 133, Section 3.4.7.5 The EAG incorrectly note the appraisal ID of talquetamab, as "TA5082", instead of "ID5082".	Please amend the following statements as follows: • "The company adopted lognormal modelling (for OS, PFS, and TTD) on the assumption that TA1015 procedures were desirable for, and applicable to, **ID**~~TA~~5082.". • "Unlike TA1015, in **ID**~~TA~~5082 the company owns IPD for both comparators not just one.".	Update to ensure the ID for the appraisal of talquetamab is correctly presented.	
Page 133, Section 3.4.7.5 The EAG incorrectly note that "Unlike TA1015, in TA5082 the company owns IPD for both	J&J IM request that this statement is removed from the EAG report.	As noted in Section B.2.9 of the CS for teclistamab in TA1015, J&J IM had access to the IPD in this analysis from real-world	Amended

comparators not just one. As such the company can explore many options not just that predicated on the previous TA for teclistamab versus Pom-Dex.”.		data that informed the efficacy of PomDex.[7] Update to remove factually inaccurate statement.	
Page 134, Section 3.4.7.5 The text incorrectly states that the ITC OS HR is [redacted]	Correct value from [redacted] to [redacted]	Value should be corrected as per Table 32 of the Company submission.	Amended
Page 135, Section 3.4.7.5 The text incorrectly states that the ITC OS HR is [redacted]	Correct value from [redacted] to [redacted]	Value should be corrected as per Table 32 of the Company submission.	Amended
Page 143, Section 3.4.10.4 The is a typographical error in the statement “In the economic model, [redacted] of patients in the talquetamab arm and [redacted] of patients in the teclistamab arm were modelled to receive subsequent therapies following disease progression for an average duration of 4	Correct “Young” to “**Yong**”.	The author of the study was Yong. Update typographical error to ensure author’s name is spelled correctly.	Amended

months, in line with Young et al. (2016) and NICE committee preferences in TA1015.[7, 22]".			
Page 145, Section 3.4.11 The EAG incorrectly note that "The company calculated the absolute and proportional QALY shortfalls for people with RRMM who had received four prior therapies".	Please amend the text as follows: "The company calculated the absolute and proportional QALY shortfalls for people with **TCE** RRMM ~~who had received four prior therapies~~".	The population included in the calculation were patients with TCE RRMM, and as such had received at least three prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody (mAb) and have demonstrated disease progression on their last therapy. This should be updated to ensure the correct patient population is referred to.	Amended
Page 146, Section 3.4.12, Table 42 The EAG incorrectly state that "Talquetamab OS, PFS and TTD is modelled by applying the OS HR estimated from ITC for talquetamab versus teclistamab (post-two stage adjustment for OS)	Please amend the text as follows: "Talquetamab OS, PFS and TTD is modelled by applying the ~~OS~~ **respective** HR**s** estimated from **the** ITC for talquetamab versus teclistamab (post-two stage adjustment for OS) to the teclistamab extrapolation described above.".	The talquetamab OS, PFS and TTD extrapolations were modelled by applying the respective HRs from the ITC for talquetamab vs. teclistamab, not just the OS HR. This should be updated to ensure the modelling	Amended

to the teclistamab extrapolation described above.".		approach is correctly detailed.	
Page 158, Section 4.2.1 The text incorrectly states that "talquetamab has a [redacted] probability of being cost-effective compared to teclistamab at a willingness-to-pay threshold of £30,000 per QALY".	Please amend the text as follows: "talquetamab has a [redacted]-probability of being cost-effective compared to teclistamab at a willingness-to-pay threshold of £~~3~~**2**0,000 per QALY".	Values should be corrected as per Company submission section 3.11.1.	Amended
Page 159, Section 4.2.1, Table 45 The table incorrectly states that the teclistamab total costs are [redacted]	Correct the value from £[redacted] to [redacted]	Value should be corrected as per Table 76 of the Company submission.	Amended
Page 164, Section 4.2.2.1.1 Table 47 The table incorrectly states that the base-case ICER is [redacted]	Correct the value from £[redacted] to [redacted]	Value should be corrected as per Table 77 of the Company submission.	Amended
Page 175, Section 5.1, Table 50 In the AEs disutility row, the EAG note that the Company's value is	Please amend the text as follows: "The company's base-case analysis i**ncludes AE disutilities**".	This statement does not currently make sense and does not capture how AE disutility was incorporated in the model. This should	Amended

informed by “The company’s base-case analysis.”.		be updated to state that AE disutilities were included in the Company’s base case analysis.	
Page 175, Section 5.1, Table 50 and Page 177, Section 5.3 The EAG state that “The EAG consider that the inclusion disutilities associated with adverse events may result in double counting.”	Please amend the text as follows: “The EAG consider that the inclusion **of** disutilities associated with adverse events may result in double counting. **As such the EAG excluded AE disutilities in their base-case model**.”.	It is currently unclear whether the EAG excluded adverse event disutilities in their base case analysis. This statement should therefore be updated to improve clarity.	Amended
Page 187, Section 5.6 The EAG incorrectly note that “The company’s model draws on survival evidence from the MajesTEC-1 trial (talquetamab)”.	Please amend the text as follows: “The company’s model draws on survival evidence from the MajesTEC-1 trial (~~talquetamab~~ **teclistamab**).	The survival evidence from the MajesTEC-1 trial is for teclistamab, not talquetamab. Update to ensure the correct treatment is referred to.	Amended
Page 187, Section 5.6 It is noted that J&J IM’s economic model “assumed proportional hazards based on their ITC of two single-arm studies to obtain survival	Please amend the text as follows: “assumed proportional hazards based on their ITC of two single-arm studies (**MonumenTAL-1 and MajesTEC-1**) to obtain survival for talquetamab OS, PFS and TTD.”.	J&J IM request that the EAG clarify which single arm studies are referred to here to improve clarity.	Amended

for talquetamab OS, PFS and TTD.”			

Confidentiality highlighting inaccuracies

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 22, Executive Summary	The modelling of a greater number of patients surviving with talquetamab than teclistamab does not require CiC highlighting, as per the CS (Section 3.3)	Because the submission models more patients survive in the talquetamab arm than the teclistamab arm this infers **greater** routine use of IVIg in the talquetamab arm.	CiC highlighting removed
Page 37, Section 1.2 Page 44, Section 2.1.3.1.1	September 2024 does not require CiC highlighting as per the updated confidentiality marking in the	Page 37, Section 1.2 However, as mentioned in CS Section 3.4.2, the EuroQoL Five Dimension Five Level Questionnaire (EQ-5D-5L) descriptive scores from MonumenTAL-1 (**September** 2024 data cut-off) were mapped onto the 3L UK value set to inform the economic model Page 44, Section 2.1.3.1.1	

Page 49, Section 2.1.4, Table 10 Page 53, Section 2.2.1.1 Page 57, Section 2.2.1.3, Table 14 Page 60, Section 2.2.2 Page 61, Section 2.2.2.1.2 Page 83, Section 2.2.6, Table 23 Page 95, Section 2.4 Page 101, Section 3.4.1, Table 26	CS as this information is published in Rasche, *et al.* 2025.[15]	As of the **September** 2024 data cut off (DCO), **17.5**% of patients remained on talquetamab treatment. Page 49, Section 2.1.4, Table 10 The company noted that the write-up of PRO data from the **September** 2024 DCO was not available in time for the submission deadline,… Page 53, Section 2.2.1.1 MonumenTAL-1 commenced in 2018, and the data provided in the CS are based on a pre-specified DCO of **September** 2024. Page 57, Section 2.2.1.3, Table 14 In the row for "duration of study follow-up": **September** 2024 DCO Page 60, Section 2.2.2 MonumenTAL-1 (Cohort C n=**154**; **September** 2024 DCO) In the MonumenTAL-1 trial (on **September** 2024 DCO), [redacted]/154 ([redacted]%) of the study participants did not complete the study, of whom [redacted] ([redacted]%) died, [redacted] ([redacted]%) withdrew consent, [redacted] ([redacted]%) started subsequent anti-cancer therapy, and 1 (0.6%) was lost to follow-up (CS Table 9). Page 61, Section 2.2.2.1.2 The company stated that PROs such as HRQoL from the **September** 2024 DCO were not available in time for the submission deadline… Page 83, Section 2.2.6, Table 23 Title for Table 23: Adverse events for talquetamab (MonumenTAL-1; Cohort C; **September** 2024 DCO) and teclistamab (MajesTEC-1; August 2023 DCO) [adapted from CS Tables 41-49]. Page 95, Section 2.4	

Page 104, Section 3.4.3, Table 27 Page 105, Section 3.4.3, Table 28 Page 121, Section 3.4.7.1 Page 135, Section 3.4.7.5 Page 136, Section 3.4.9, Table 33		The company selected one (of 3) Cohorts from MonumenTAL-1 for inclusion in this appraisal. (Cohort C n=154**; September** 2024 DCO). MonumenTAL-1, Cohort C n=**154**; **September** 2024 DCO Page 101, Section 3.4.1, Table 26 MonumenTAL-1 Cohort C (**September** 2024 DCO) Page 104, Section 3.4.3, Table 27 Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (**September** 2024 DCO) Page 105, Section 3.4.3, Table 28 Source: J&J IM. Data on File. MonumenTAL-1 Clinical Study Report (**September** 2024 DCO) Page 121, Section 3.4.7.1 The treatments listed were received within the **September** 2024 data cut-off, by which time the observed OS extends to about [redacted] follow-up. Page 135, Section 3.4.7.5 The modelled post-progression survival for talquetamab treatment could be due to lingering post-treatment effectiveness of talquetamab, as well as to the receipt of effective fifth line subsequent treatments (those reported were received before the cut off **September** 2024) Page 136, Section 3.4.9, Table 33 MonumenTAL-1 trial (**September 2024** DCO, CS model [lowest AIC])	
Page 41, Section 2.1.2.1.1	The range of the number of participants randomised or enrolled in 23 studies does not require CiC highlighting, as	The number of participants randomised or enrolled in 23 studies ranged from **14-288**.	CiC marking removed

	per CS (Appendix B.1.3)		
Page 42, Section 2.1.3.1.1	The median age of patients in MonumenTAL-1 Cohort C is published and does not require CiC highlighting, as per the CS (Section 2.3.3)	Most patients were white (81.8%) with a median age of **67** years.	
Page 43, Section 2.1.3.1.1 Page 44, Section 2.1.3.1.1 Page 60, Section 2.2.2 Page 73, Section 2.2.5.1.1 Page 95, Section 2.4	The number of patients in Cohort C of MonumenTAL-1 (N=154) and patients in MajesTEC-1 (N=165) does not require CiC highlighting, as per the CS (Section 2.3.3, Section 2.10.3)	Page 43, Section 2.1.3.1.1 In Cohort C, **154** patients received 0.8 mg/kg talquetamab every two weeks. Page 44, Section 2.1.3.1.1 Consequently, the company selected Cohort C IPD (n=**154**) from the MonumenTAL-1 study to provide the evidence for talquetamab in the ITC analysis which is critiqued in Section 2.2. Page 60, Section 2.2.2 In the MonumenTAL-1 trial (on September 2024 DCO), [redacted]**/154.** Page 73, Section 2.2.5.1.1 All patients included in the ITC analysis had outcome data reported, and no patients were excluded from the analysis based on missing data. Efficacy analyses included all **165** participants in the All Treated Analysis Set of the MajesTEC-1 IPD and all 154 patients in MonumenTAL-1 trial IPD. Page 95, Section 2.4	CiC marking amended

Page 108, Section 3.4.6		The company selected one (of 3) Cohorts from MonumenTAL-1 for inclusion in this appraisal. (Cohort C n=**154**; September 2024 DCO). AND The company's adjusted (ATT-adjusted IPTW-based) ITC analysis was informed by IPD sets from two Cohorts in MonumenTAL-1 and MajesTEC-1: • MonumenTAL-1, Cohort C n=**154**; September 2024 DCO • MajesTEC-1, All Treated Analysis Set n=**165**; August 2023 DCO Page 108, Section 3.4.6 The company presents Kaplan-Meier analyses for **154** talquetamab recipients from the MonumenTAL-1 and **165** teclistamab recipients from the MajesTEC -1 studies. Of the **165** patients in the teclistamab TCR group at least [redacted] was from UK and follow-up was approximately [redacted] months.	
Page 43, Section 2.1.3.1.1	The qualitative comparison of the baseline characteristics of patients in MonumenTAL-1 and MajesTEC-1 do not require CiC highlighting as per the CS (Section 2.3.3). This includes words such as "lower", "greater" and "higher".	CiC marking can be removed from the following statements: • Company clinical experts also suggested that every two weeks dosing in Cohort C is associated with a **lower** incidence of adverse events than in Cohort A who experienced weekly SC dosing (CS Section: 2.11 section and Appendix L). • **Greater** proportion of patients aged ≥75 in the MonumenTAL-1 study than in the MajesTEC-1 • **Higher** proportion of patients with International Staging System ([ISS] classification system) stage III disease	CiC marking amended

Page 43, Section 2.1.3.1.1	The median lines of therapy of patients in MonumenTAL-1 Cohort C is published and does not require CiC highlighting, as per the CS (Section 2.3.3)	However, it is worth noting that the prior lines of therapy in Cohort C ranged from [redacted], with a median of **4.5.**	
Page 43, Section 2.1.3.1.1	The proportion of patients aged ≥75 in MajesTEC-1 does not require CiC highlighting as per the CS (Section 2.3.3)	([redacted]% compared to **14.5**%, respectively).	CiC marking amended
Page 44, Section 2.1.3.1.1	The proportion of patients in MonumenTAL-1 Cohort B who received prior CAR-T therapies is published and does not require CiC highlighting, as	Cohort B has its own limitation as this group includes patients with prior TCR exposure (**73.1**% received CAR-T therapies)	

	per the CS (Section 2.3.3)		
Page 44, Section 2.1.3.1.1	The proportion of patients with International Staging System stage III disease in both MonumenTAL-1 and MajesTEC-1 does not require CiC highlighting as per the CS (Section 2.3.3)	(**24.4**% in MonumenTAL-1 compared to **12.3**% in MajesTEC-1).	
Page 44, Section 2.1.3.1.1	The proportion of patients with International Staging System stage III disease in MajesTEC-1 does not require CiC highlighting as per the CS (Section 2.3.3)	([redacted]% in MonumenTAL-1 compared to **12.3**% in MajesTEC-1).	CiC marking amended
Page 44, Section 2.1.3.1.1	The proportion of patients with extramedullary plasmacytomas	([redacted]% had ≥1 in the MonumenTAL-1 study compared to **17.0**% in the MajesTEC-1 study).	CiC marking amended

	in MajesTEC-1 does not require CiC highlighting as per the CS (Section 2.3.3)		
Page 49, Section 2.1.5	The total number of patients in MonumenTAL-1 experiencing at least one treatment-emergent adverse event (TEAE) highlighting in alignment with the CS (Section 2.11.2)	[redacted] patients in Cohort C of the MonumenTAL-1 trial (cohort considered relevant to this appraisal) experienced at least one treatment-emergent adverse event (TEAE), with [redacted]% of patients experiencing at least one TEAE that was related to talquetamab.	CiC marking amended
Page 49, Section 2.1.5 Page 83, Section 2.2.6 Page 85, Section 2.2.6	The qualitative comparison of the adverse events in MonumenTAL-1 and MajesTEC-1 do not require CiC highlighting as per the CS (Section 2.11). This includes	Page 49, Section 2.1.5 The company acknowledged that the number of TEAEs leading to discontinuation, Grade 4 AEs, Grade 5 AEs and TEAEs leading to death were **higher** in Cohort C compared to Cohort A. However, the overall incidence of TEAEs related to talquetamab, serious TEAEs, serious TEAEs related to talquetamab and Grade 1–3 TEAEs were **lower** in Cohort C compared to Cohort A. Page 83, Section 2.2.6 The following statements should be updated:	CiC marking amended

Page 87, Section 2.2.6.1.1 Page 88, Section 2.2.7 Page 96, Section 2.4	words such as “lower”, “greater” and “higher”.	• The proportion of patients with at least one Grade 3/4 TEAE was **greater** in MajesTEC-1 (teclistamab) versus MonumenTAL-1 (talquetamab) • In contrast, **more** patients with talquetamab than teclistamab experienced the AESIs of any grade Accordingly, the dose modification (delay, modification, skip) was **more** frequent in teclistamab compared to talquetamab Page 85, Section 2.2.6 The following statements should be updated: • The proportion of all-cause deaths was **greater** for patients in the teclistamab versus talquetamab • The proportion of patients who died due to disease progression was **greater** in teclistamab **Likewise**, more patients in teclistamab versus talquetamab arm died due to infection-related causes Page 87, Section 2.2.6.1.1 The ITC results indicate that talquetamab demonstrated **comparable** (for CRS, AEs of Metabolic/Nutrition disorders System Organ Class/SOC) or a **better** safety (for total grade 3-4 TEAEs, AEs of Blood/Lymphatic System Disorders SOC, any grade infections, grade 3/4 infections, fatal infections) profile compared to teclistamab. In contrast, teclistamab compared to talquetamab showed **better** safety profile for ICANS and GPRC5D-specific AEs (e.g., dysgeusia, weight loss, skin disorders, rash and nail disorders). The GPRC5D-specific AEs are **less severe** and thus easier to manage their risk. Furthermore, the reduction in grade 3/4 infections associated with talquetamab correlate with a reduced intravenous immunoglobulin (IVIg) use. The EAG suggest that given the AE evidence provided in the trials, talquetamab showed a **better** safety profile compared to teclistamab.	

		Page 88, Section 2.2.7 There were **more** infection-related deaths in teclistamab versus talquetamab Page 96, Section 2.4 There were **more** infection-related deaths in teclistamab versus talquetamab	
Page 50, Section 2.1.5	The number of prior lines received by patients in Cohort B of MonumenTAL-1 does not require CiC highlighting, as per the CS (Appendix L.1)	Cohort B included more heavily pre-treated patients who had experienced **more than five lines** of treatment and was not open for enrolment.	Amended from previous correction.
Page 50, Section 2.1.5.1 Page 57, Section 2.2.1.3, Table 14 Page 58, Section 2.2.1.3 Page 60, Section 2.2.2	The median follow-up of MajesTEC-1 and MonumenTAL-1, and their corresponding data cut-offs has been published and as such do not require CiC highlighting, in line with Section 2.3.2	Page 50, Section 2.1.5.1 This was based on the final prespecified DCO of **August** 2023, with a median follow-up of **30.4** months, which also informed TA1015 (See Table 7). Page 57, Section 2.2.1.3, Table 14 Duration of study follow up row: • The first patient in the study was treated on 3rd January 2018 and at the latest DCO the median duration of follow-up was **31.2** months for Cohort C (n=154) • The first patient in the study was treated on 16th May 2017, and at the latest DCO, the median duration of follow-up: **30.4** months (range: **0.3-41.5** months) for the All Treated Analysis Set (n=165). Page 58, Section 2.2.1.3	

<table>
<tr>
<td>Page 76, Section 2.2.5.1.3

Page 95, Section 2.4</td>
<td>(MonumenTAL-1 follow-up) and Section 2.10 (MajesTEC-1 follow-up) of the updated CS</td>
<td>In terms of the outcome assessment, the length of follow-up was sufficient and similar between the two trials (median: 30-31 months).

Page 60, Section 2.2.2

• MajesTEC-1 (All Treated Analysis Set n=165; August 2023 DCO).

• In the MajesTEC-1 trial (on August 2023 DCO)

Page 76, section 2.2.5.1.3

after the median follow-up of 31.2 months and 30.4 months, respectively.

Page 95, Section 2.4

MajesTEC-1, All Treated Analysis Set n=165; August 2023 DCO.</td>
<td></td>
</tr>
<tr>
<td>Page 52, Section 2.2.1.1</td>
<td>The sample size breakdown of the patients enrolled in each Phase of MonumenTAL-1 by Cohort requires CiC highlighting in alignment with the CS (Section 2.3.1)</td>
<td>
<table>
<tr><th>Patient cohort, prior TCR exposure</th><th>Dose of talquetamab</th><th>Phase, part # (sample size)</th></tr>
<tr><td>Cohort A - No prior TCR exposure</td><td>0.4 mg/kg weekly SC</td><td>Phase I, part 2 (n=[redacted])
Phase II, part 3 (n=[redacted])
Total sample (n=143)</td></tr>
<tr><td>Cohort B - Prior TCR exposure</td><td>0.4 mg/kg weekly SC or 0.8 mg/kg every two weeks SC</td><td>Phase I, part 2 (n=[redacted])
Phase II, part 3 (n=[redacted])
Total sample (n=78)</td></tr>
<tr><td>Cohort C - No prior TCR exposure</td><td>0.8 mg/kg every two weeks SC</td><td>Phase I, part 2 (n=[redacted])
Phase II, part 3 (n=[redacted])
Total sample (n=154)</td></tr>
</table>
</td>
<td>CiC marking amended</td>
</tr>
<tr>
<td>Page 52, Section 2.2.1.2</td>
<td>The MajesTEC-1 overall sample sizes have been published and</td>
<td>MajesTEC-1 consisted of three cohorts A, B and C (see Section 2.1.5.1) the IPD from the ‘All Treated Analysis Set’ sample (N=165), i.e., the combination of Cohort A (n=125) and the RP2D sample (n=40) from Phase I (part 2) were used to inform the assessment of comparative clinical efficacy for teclistamab versus talquetamab in the ITC analysis (Table 13).</td>
<td>CiC marking amended</td>
</tr>
</table>

<table>
<tr><td></td><td>do not require CiC highlighting</td><td></td><td></td></tr>
<tr><td>Page 57, Section 2.2.1.3, Table 14

Page 79, Section 2.2.5.1.5, Table 21

Page 103, Section 3.4.3, Table 27</td><td>The number of patients receiving subsequent treatment in MonumenTAL-1 and MajesTEC-1 require CiC highlighting in alignment with the CS (Section 2.10.4)</td><td>
<table>
<tr><th>Study feature</th><th>MonumenTAL-1 trial (Talquetamab) IPD
Phase I (NCT03399799)
Phase II (NCT04634552)
[n=154]</th><th>MajesTEC-1 trial (Teclistamab) IPD
Phase I (NCT03145181)
Phase II (NCT04557098)
[n=165]</th><th>Comparability (EAG assessment: Yes or No)</th></tr>
<tr><td>Subsequent treatments (most frequent)</td><td>N=[redacted]

<u>UK relevant</u>
Teclistamab [redacted]

<u>Non-UK relevant</u>
Carfilzomib + chemotherapy [redacted]
Belantamab-based regimens [redacted] CAR-T cell therapies [redacted]
Dexamethasone-based regimens [redacted]</td><td>N=[redacted]

<u>UK relevant</u>
Bortezomib + chemotherapy [redacted]

<u>Non-UK relevant</u>
Investigational antineoplastic drugs ([redacted] Talquetamab [redacted] Pomalidomide based regimens [redacted]
Carfilzomib + chemotherapy [redacted]
CAR-T cell therapies [redacted]</td><td>No</td></tr>
</table>
Page 79, Section 2.2.5.1.5, Table 21
<table>
<tr><th>Patients receiving subsequent therapy (%)</th><th>Before subsequent treatment adjustment</th><th>After adjustment (re-weighting) for subsequent treatment (Base case scenario)</th></tr>
</table>
</td><td>CiC marking amended</td></tr>
</table>

		<table><tr><th></th><th>Talquetamab (MonumenTAL-1; Cohort C) N=[redacted][a]</th><th>Teclistamab (MajesTEC-1) N=[redacted][b]</th><th>Talquetamab (MonumenTAL-1; Cohort C)[c]</th><th>Teclistamab (MajesTEC-1)[c]</th></tr></table> Page 103, Section 3.4.3, Table 27 Talquetamab (MonumenTAL-1; Cohort C [N=[redacted][a]]). Teclistamab (MajesTEC-1 [N=[redacted][b]])
Page 68, Section 2.2.4, Table 17	Some of the MonumenTAL-1 and MajesTEC-1 baseline characteristics before/after adjustment do not require CiC highlighting as per the CS (Table 25; Section 2.10.3))	<table><tr><th></th><th colspan="3">Before adjustment</th><th colspan="2">After adjustment</th></tr><tr><th></th><th>Talquetamab 0.8 mg/kg Q2W</th><th>Teclistamab 1.5 mg/kg SC Q1W</th><th>SMD</th><th>Teclistamab 1.5 mg/kg SC Q1W</th><th>SMD</th></tr><tr><td>Sample size</td><td>N=154</td><td>N=165</td><td></td><td>N=165</td><td></td></tr><tr><td colspan="6">Refractory status, n (%)</td></tr><tr><td>≤ Double refractory</td><td>[redacted]</td><td>[redacted]</td><td rowspan="4">[redacted]</td><td>[redacted]</td><td rowspan="4">[redacted]</td></tr><tr><td>Triple refractory</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Quad refractory</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>≥ Penta refractory</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td colspan="6">ISS</td></tr><tr><td>I</td><td>69 (44.8)</td><td>[redacted]</td><td rowspan="3">[redacted]</td><td>[redacted]</td><td rowspan="3">[redacted]</td></tr><tr><td>II</td><td>48 (31.2)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>III</td><td>37 (24)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td colspan="6">Time to progression on prior therapy</td></tr><tr><td><3 months</td><td>[redacted]</td><td>[redacted]</td><td rowspan="2">[redacted]</td><td>[redacted]</td><td rowspan="2">[redacted]</td></tr><tr><td>≥3 months</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>	

		Number of prior LOTs, n (%)						
		≤4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		≥5	[redacted]	[redacted]		[redacted]		
		ECOG performance status, n (%)						
		0	58 (37.7)	55 (33.3)	[redacted]	[redacted]	[redacted]	
		1+	96 (62.3)	110 (66.7)		[redacted]		
		Age, n (%)						
		<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		≥65	[redacted]	[redacted]		[redacted]		
		Gender, n (%)						
		Male	90 (58.4)	96 (58.2)	[redacted]	[redacted]	[redacted]	
		Female	64 (41.6)	69 (41.8)		[redacted]		
		Prior autologous stem cell transplantation, n (%)						
		Yes	121 (78.6)	135 (81.8)	[redacted]	[redacted]	[redacted]	
		No	33 (21.4)	30 (18.2)		[redacted]		
		Time (years) since diagnosis, n (%)						
		<6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		≥6 years	[redacted]	[redacted]		[redacted]		
		Average duration of prior lines of therapy (months), n (%)						
		<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		10 to 14	[redacted]	[redacted]		[redacted]		
		≥15	[redacted]	[redacted]		[redacted]		
		Haemoglobin, n (%)						
		<12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		12+	[redacted]	[redacted]		[redacted]		
		LDH, n (%)						

		<280	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		>280	[redacted]	[redacted]		[redacted]		
		Creatinine clearance, n (%)						
		<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		60-<90	[redacted]	[redacted]		[redacted]		
		90+	[redacted]	[redacted]		[redacted]		
		MM type, n (%)						
		IgG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		Non-IgG	[redacted]	[redacted]		[redacted]		
		Race, n (%)						
		White	126 (81.8)	134 (81.2)	[redacted]	[redacted]	[redacted]	
		Other/not reported	28 (18.2)	31 (18.8)		[redacted]		
		Cytogenetic risk, n (%)						
		Standard risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		High risk	[redacted]	[redacted]		[redacted]		
		Missing	[redacted]	[redacted]		[redacted]		
		EMD, n (%)						
		Yes	41 (26.6)	28 (17.0)	[redacted]	[redacted]	[redacted]	
		No	113 (73.4)	137 (83.0)		[redacted]		
		ASCT=autologous stem cell transplantation; ECOG=Eastern Cooperative Oncology Group; EMD=extramedullary plasmacytoma; IgG=immunoglobulin-G; ISS=International Staging System; LDH=lactate dehydrogenase; LOT=line of treatment; MM=multiple myeloma; SMD=standardised mean difference; Q2W=once every two weeks; QW=once weekly						

Page 70, Section 2.2.4, Figure 2	The SMD plot between MonumenTAL-1 Cohort C (0.8 mg/kg twice weekly) and MajesTEC-1 cohorts, before and after adjustment [CS Figure 14] requires CiC highlighting in alignment with the CS (Section 2.10.3)	[redacted]		CiC marking amended

Page 71, Section 2.2.4, Figure 3	The distribution of PSs before weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort [Figure 15, the main submission document] requires CiC highlighting in alignment with the CS (Section 2.10.3)	[redacted]		CiC marking amended

Page 72, Section 2.2.4, Figure 4	The distribution of PSs after ATT weighting for patients in MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) and MajesTEC-1 cohort (Figure 16, the main submission document) requires CiC highlighting in alignment with the CS (Section 2.10.3)	[redacted]	CiC marking amended
Page 73, Section 2.2.5.1.2 Page 74, Section 2.2.5.1.3 Page 75, Section 2.2.5.1.3 Page 76, Section 2.2.5.1.3	The qualitative description of the ITC results comparing talquetamab and teclistamab and the direction of the OS benefit does not require CiC highlighting as per the CS (Section 2.10)	Page 73, Section 2.2.5.1.2 Results indicate that patients in the talquetamab arm had a **significantly improved** ORR compared to patients in the teclistamab arm (RR=[redacted]). In contrast, there was **no statistically significant** difference between talquetamab and teclistamab in the proportion of patients achieving ≥CR (RR=[redacted]) or ≥VGPR (RR=[redacted]). Page 74, Section 2.2.5.1.3 The median DOR for talquetamab ([redacted] months; 95% CI: [redacted]) was **shorter** compared to the ATT-adjusted teclistamab Page 75, Section 2.2.5.1.3	CiC marking amended

Page 78, Section 2.2.5.1.4 Page 82, Section 2.2.5.1.5 Page 87, Section 2.2.7 Page 88, Section 2.2.7 Page 89, Section 2.2.7 Page 90, Section 2.2.7 Page 92, Section 2.2.7.1 Page 93, Section 2.3 Page 94, Section 2.3 Page 95, Section 2.4		The KM PFS curves suggested **comparable** efficacy of talquetamab. Page 76, Section 2.2.5.1.3 The OS KM curves presented in Figure 7 indicate that patients receiving talquetamab experienced **greater** median time to death. Page 78, Section 2.2.5.1.4 Similar to the main ATT-adjusted ITC analysis, patients receiving talquetamab experienced at least [redacted] statistically significant reduced risk of death compared to patients receiving teclistamab. Page 82, Section 2.2.5.1.5 The analysis showed little variation in the OS HR estimates which were consistently in favour of talquetamab over teclistamab. Page 87, Section 2.2.7 However, the magnitude of **improvement** in OS compared to PFS requires further exploration. The EAG considers that the **large** benefit, i.e., in OS in favor of talquetamab. Page 88, Section 2.2.7 It is not clear to the EAG, whether the **magnitude** of **improvement** in OS is attributable solely to the effect of talquetamab or may at least partly be due to some other extraneous factors such as unknown confounding, post-progression informative censoring, or different reasons for switching to subsequent treatments. Page 89, Section 2.2.7 • These statements are useful in helping to explore the **magnitude** of OS benefit suggested from the company ITC. • Uncertainty remains as to the reasons for the observation of relatively **large** benefit size in OS for talquetamab compared to no between-treatment group difference observed for other outcomes (CR, VGPR, DoR).	

Page 96, Section 2.4 Page 118, Section 3.4.7 Page 122, Section 3.4.7.1 Page 135, Section 3.4.7.5		Page 90, Section 2.2.7 The observed benefit in OS could be explained by the alternative biologic mechanism (different MM cell target and downstream effects) through which talquetamab **impedes** the occurrence of life-threatening infections more effectively and safely than teclistamab. This statement is supported by the ITC results provided in Table 24 showing in patients treated with teclistamab versus talquetamab **higher** rates of infection-related deaths. Page 92, Section 2.2.7.1 This confirms the EAG concerns pertaining to the magnitude of OS **benefit** for talquetamab relative to teclistamab. Page 93, Section 2.3 The clinical **benefits** of talquetamab compared to teclistamab observed for ORR and OS may have been biased due to confounding arising from unknown or unmeasured covariates which are independently associated with the prognosis of RRMM. Page 94, Section 2.3 • Additional uncertainty in the results stems from the inconsistent observed **benefits** for talquetamab versus teclistamab across the ITC reported outcomes (See Table 22). For example, in contrast to the observed differences in ORR and OS **in favour** of talquetamab versus teclistamab, there were **no significant** differences between the two treatments for the remaining outcomes of very good partial response [≥VGPR], complete response [≥CR], duration of response [DOR], and PFS. Selecting and reporting only those outcomes with significant differences in **favour** of the intervention (talquetamab) will overestimate the overall beneficial effect of treatment. Page 95, Section 2.4 • The adjusted ITC results (base case scenario) suggest significant **improvements** in the overall response rate (ORR; [redacted]% **improvement**) and OS ([redacted]% **reduction** in the hazard of death) **in** favour of talquetamab compared to teclistamab.	

		○ All other ITC outcomes (very good partial response [≥VGPR], complete response [≥CR], duration of response, and progression-free survival), indicated **no significant difference** between the two treatments. Page 96, Section 2.4 The EAG consider the benefit in OS **in favour** of talquetamab may have been overestimated if this or other differences were not accounted for in the analyses. Page 118, Section 3.4.7 Although PFS is **similar** between arms (ITC HR = [redacted]), talquetamab OS is **superior** to teclistamab OS (reported unadjusted HR = [redacted], adjusted HR = [redacted] and ITC HR = [redacted]). This suggests that even over the short observation period of approximately 36 months there is **considerable survival benefit** in the talquetamab arm relative to teclistamab arm and that much of this extra **benefit** occurs after progression (black dashed arrow); in contrast, for teclistamab, post-progression survival benefit is **modest** relative to pre-progression survival. Page 122, Section 3.4.7.1 there was a clear OS **benefit** to talquetamab. Potential reasons were discussed in Section 2.2.7. However the large OS gain for talquetamab over teclistamab is driven by the application of the ITC HR of [redacted] that appears dependent on an underestimate of teclistamab survival (lack of correction for influence of COVID on unvaccinated MajesTEC-1 participants. The **greater** post-progression survival **benefit** from talquetamab versus teclistamab is seen after extrapolation modelling to life-time horizon (see Figure 25). Page 135, Section 3.4.7.5 The company's modelling of OS for patients in receipt of talquetamab treatment generated a large proportion of survival **gain** accruing after progression and after cessation of talquetamab treatment.	

<table>
<tr><td></td><td></td><td>This was in contrast to teclistamab where practically no survival benefit accrued after progression; it is problematical to explain this solely based on lingering effectiveness of talquetamab for decades after cessation of talquetamab treatment.</td><td></td></tr>
<tr><td>Page 73, Section 2.2.5.1.2, Table 18</td><td>The response rates for MajesTEC-1 following ATT weighting require CiC highlighting in alignment with the CS (Section 2.6.1 and Section 2.10.5)</td><td>
<table>
<tr><th rowspan="2">Response outcome [Tal vs. Tec]</th><th colspan="2">Before ATT weighting (observed)</th><th colspan="2">After ATT weighting (adjusted)</th></tr>
<tr><th>MonumenTAL-1 Tal 0.8 mg/kg every two weeks</th><th>MajesTEC-1 Tec 1.5 mg/kg weekly</th><th>MonumenTAL-1 Tal 0.8 mg/kg every two weeks</th><th>MajesTEC-1 Tec 1.5 mg/kg weekly</th></tr>
<tr><td colspan="5">ORR</td></tr>
<tr><td>(%)</td><td>69.5</td><td>63.0</td><td>69.5</td><td>[redacted]</td></tr>
<tr><td>RR (95% CI); p-value</td><td colspan="2">[redacted]</td><td colspan="2">[redacted]</td></tr>
<tr><td colspan="5">≥VGPR</td></tr>
<tr><td>(%)</td><td>59.1</td><td>59.4</td><td>59.1</td><td>[redacted]</td></tr>
<tr><td>RR (95% CI); p-value</td><td colspan="2">[redacted]</td><td colspan="2">[redacted]</td></tr>
<tr><td colspan="5">≥CR</td></tr>
<tr><td>(%)</td><td>40.3</td><td>46.1</td><td>40.3</td><td>[redacted]</td></tr>
<tr><td>RR (95% CI); p-value</td><td colspan="2">[redacted]</td><td colspan="2">[redacted]</td></tr>
<tr><td colspan="5">ATT=average treatment effect for the treated population; CI=confidence interval; CR=complete response; ITC=indirect treatment comparison; ORR=overall response rate; RR=relative risk; VPGR: very good partial response; Tal talquetamab; Tec=teclistamab; Q2W=once every two weeks; QW=once weekly</td></tr>
</table>
</td><td></td></tr>
<tr><td>Page 74, Section 2.2.5.1.3</td><td>The 95% CI for the DOR ITC results comparing talquetamab</td><td>The median DOR for talquetamab ([redacted] months; 95% CI: [redacted]) was shorter compared to the ATT-adjusted teclistamab ([redacted] months; 95% CI: [redacted]).</td><td>CiC marking amended</td></tr>
</table>

	and teclistamab requires CiC highlighting in alignment with the CS (Section 2.10.5)		
Page 75, Section 2.2.5.1.3	Figure 5, the DOR KM curves for talquetamab and teclistamab (before and after ATT weighting) [CS Figure 18] requires CiC highlighting in alignment with the CS (Section 2.10.5)	[redacted]	CiC marking amended
Page 76, Section 2.2.5.1.3	The median time to death in MonumenTAL-1 has been published and therefore, does not require CiC highlighting in	The OS KM curves presented in Figure 7 indicate that patients receiving talquetamab experienced [redacted] median time to death (**not estimable, 95% CI: not estimable, not estimable**).	

	alignment with the CS (Section 2.11.4)		
Page 81, Section 2.2.5.1.5, Figure 8	Figure 8, the OS KM curves for talquetamab and ATT-weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice (base case scenario) [CS Figure 21] requires CiC highlighting in alignment with the CS (Section 2.10.5)		CiC marking amended
Page 83, Section 2.2.6 Page 83, Section 2.2.6, Table 23	Some AESIs from MonumenTAL-1 Cohort C do not require CiC highlighting as per the CS, Section 2.11.4	Page 83, Section 2.2.6 ICANS ([redacted]% vs. [redacted]%), Dysgeusia (**72.1**% vs. [redacted]%) weight loss (**41.6**% vs. [redacted]%), skin disorders (**73.4**% vs. [redacted]%), rash (**31.2**% vs. [redacted]%), and nail disorders (**54.5** vs[redacted]More patients after teclistamab compared to talquetamab experienced infection of any grade ([redacted]% vs. **70.8%**), Grade 3/4 ([redacted]% vs. [redacted]%), and infection with fatal outcome ([redacted]vs. [redacted]). Page 83, Section 2.2.6, Table 23	

Adverse event N (%)	MonumenTAL-1 Cohort C [N=154]	MajesTEC-1 [N=165]
	Talquetamab (0.8 mg/kg Q2W)	Teclistamab (1.5 mg/kg Q1W)
ICANS (any grade)	[redacted]	[redacted]
Grade 3/4	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Dysgeusia (any grade)	**111 (72.1)**	[redacted]
Grade 3/4	**0**	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Weight loss (any grade)	**64 (41.6)**	[redacted]
Grade 3/4	**9 (5.8)**	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]
Skin disorders (any grade)	**113 (73.4)**	[redacted]
Grade 3/4	**1 (0.6)**	[redacted]
Leading to drug discontinuation	[redacted]	[redacted]
Leading to dose modification[a]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]
Outcome of fatal	[redacted]	[redacted]

		Rash (any grade)	**48 (31.2)**	[redacted]
		Grade 3/4	**8 (5.2)**	[redacted]
		Leading to drug discontinuation	[redacted]	[redacted]
		Leading to dose modification[a]	[redacted]	[redacted]
		Leading to dose reduction	[redacted]	[redacted]
		Outcome of fatal	[redacted]	[redacted]
		Nail disorders (any grade)	**84 (54.5)**	[redacted]
		Grade 3/4	**0**	[redacted]
		Leading to drug discontinuation	[redacted]	[redacted]
		Leading to dose modification[a]	[redacted]	[redacted]
		Leading to dose reduction	[redacted]	[redacted]
		Outcome of fatal	[redacted]	[redacted]
		Infections (any grade)	**109 (70.8)**	[redacted]
		Grade 3/4	[redacted]	[redacted]
		Leading to discontinuation	[redacted]	[redacted]
		Leading to dose modification[a]	[redacted]	[redacted]
		Leading to dose reduction	[redacted]	[redacted]
		Outcome of fatal	[redacted]	[redacted]
Page 83, Section 2.2.6, Table 23	Some Grade 3/4 AEs from MonumenTAL-1 Cohort C do not require CiC highlighting as per the CS, Section 2.11.3, Table 41			

Adverse event N (%)	**MonumenTAL-1 Cohort C [N=154]**	**MajesTEC-1 [N=165]**
	Talquetamab (0.8 mg/kg Q2W)	**Teclistamab (1.5 mg/kg Q1W)**
Most common (≥5%) Grade 3 or 4 TEAEs		
Patients with ≥1 Grade 3 or 4 TEAE	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]

<table>
<tr><td></td><td></td><td><table>
<tr><td>Lymphopenia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Anaemia</td><td>39 (25.3)</td><td>[redacted]</td></tr>
<tr><td>Neutropenia</td><td>33 (21.4)</td><td>[redacted]</td></tr>
<tr><td>Thrombocytopenia</td><td>28 (18.2)</td><td>[redacted]</td></tr>
<tr><td>Leukopenia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Metabolism and Nutrition Disorders</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypokalaemia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypophosphataemia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Investigations</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Weight decreased</td><td>9 (5.8)</td><td>[redacted]</td></tr>
<tr><td>Vascular disorders</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Hypertension</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td></td></tr>
<tr><td>Page 86, Section 2.2.6</td><td>The qualitative description of the IVIg use requirement for talquetamab and teclistamab does not require CiC highlighting in alignment with the CS (Section 2.11.4)</td><td>Talquetamab is expected to reduce the need for supportive IVIg when compared to teclistamab. This appears to be supported by the evidence from MonumenTAL-1 and MajesTEC-1 trials suggesting a lower rate of IVIg use in patients after receiving talquetamab versus teclistamab.</td><td>CiC marking amended</td></tr>
<tr><td>Page 88, Section 2.2.7</td><td>The number of deaths due to COVID-19 in MajesTEC-1</td><td>Page 88, Section 2.2.7:</td><td>Some amendments made [redacted]</td></tr>
</table>

<table>
<tr>
<td>Page 89, Section 2.2.7</td>
<td>should be CiC highlighted in alignment with the CS for teclistamab (Section B.2.6.7)</td>
<td>The company highlighted that among the [redacted] death events observed at the time of data-cut off, [redacted] were due to COVID, representing nearly [redacted]% ([redacted]) of all infection-related deaths in MajesTEC-1.

On page 79 of the TA1015 CS, the company made the following statement:

“it is important to note that the MajesTEC-1 trial occurred during the height of the COVID-19 pandemic before widespread vaccinations were available – [redacted] of the [redacted] OS events in MajesTEC-1 died due to COVID-19.”.

Page 89, Section 2.2.7:

subsequently, a substantial number of patients ([redacted]/165) died due to COVID-19.</td>
<td>Others not CIC because not redacted in the TECLI CS available on internet.</td>
</tr>
<tr>
<td>Page 101, Section 3.4.1, Table 26</td>
<td>The proportion of female patients included in the model base case does not require CiC highlighting as per the CS (Page 137, Table 51)</td>
<td>
<table>
<tr><th>Model parameter</th><th>Base-case [a]</th><th>Scenario analysis [b]</th></tr>
<tr><td>Age (mean), years</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Percentage female, %</td><td>41.6</td><td>[redacted]</td></tr>
<tr><td>Weight (mean), kg</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Patient BSA (mean), m^2</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Page 102, Section 3.4.2</td>
<td>The proportion of patients receiving the Q2W and QW dosing regimens in RealiTAL is published and</td>
<td>In the base-case, in line with the RealiTAL real-world study, 88% and 12% of the participants began talquetamab on a dosing regimen of every two weeks and weekly, respectively.</td>
<td></td>
</tr>
</table>

<table>
<tr><td></td><td>do not require CiC highlighting</td><td></td><td></td></tr>
<tr><td>Pag 103, Section 3.4.3, Table 27</td><td>The caption of Table 27 does not require CiC highlighting for the word “before” in alignment with the CS (Section 2.10.4)</td><td>Table 27: Summary of subsequent treatments received by patients in MonumenTAL-1 (Cohort C) and MajesTEC-1, before subsequent treatment adjustment</td><td>CiC marking amended</td></tr>
<tr><td>Page 113, Section 3.4.6.1
Page 117, Section 3.4.6.2, Figure 20
Page 122, Section 3.4.7.1
Page 174, Section 5.1, Table 50</td><td>The ITC OS HR requires CiC highlighting in alignment with the CS (Section 2.10.5)</td><td>Page 113, Section 3.4.6.1
The ITC HR of [redacted] is applied to the teclistamab OS lognormal model that has been adjusted on clinical advice to equal 10% and 3% survivors at 10 and 15 years respectively.
Page 117, Section 3.4.6.2, Figure 20
Figure 20: Company lognormal models of talquetamab OS obtained by applying HR [redacted] (green line), 0.6 (red line) or 0.7 (black line) to the lognormal teclistamab model (lower green line).
Page 122, Section 3.4.7.1
However the large OS gain for talquetamab over teclistamab is driven by the application of the ITC HR of [redacted] that appears dependent on an underestimate of teclistamab survival (lack of correction for influence of COVID on unvaccinated MajesTEC-1 participants.
Page 174, Section 5.1, Table 50
<table>
<tr><th>Variable</th><th>Company’s Value</th><th>EAG’s value/approach</th><th>Reference to related issue in</th></tr>
<tr><td colspan="4">Clinical effectiveness</td></tr>
</table></td><td>CiC marking amended</td></tr>
</table>

<table>
<tr><td></td><td></td><td><table>
<tr><td colspan="4">Overall survival (OS)</td></tr>
<tr><td>OS</td><td>Calibrated lognormal modelling of teclistamab OS, then applying the two-stage ITC OS HR ([redacted]) to generate talquetamab OS</td><td>Uncalibrated Weibull modelling of OS</td><td>Sections 3.4.5 and 3.4.6</td></tr>
</table></td><td></td></tr>
<tr><td>Page 120, Section 3.4.7</td><td>The ITC PFS HR requires CiC highlighting in alignment with the CS (Section 2.10.5)</td><td>To obtain the base-case PFS model for talquetamab the company applied the ITC hazard ratio of [redacted] (talquetamab versus teclistamab) to the calibrated AFT lognormal PFS model for teclistamab. A superior procedure is provided by applying the [redacted] hazard ratio to the uncalibrated Weibull model.</td><td>CiC marking amended</td></tr>
<tr><td>Page 132, Section 3.4.7.4</td><td>The total number of deaths in MonumenTAL-1 patients receiving talquetamab and MajesTEC-1 patients receiving teclistamab requires CiC highlighting in alignment with the CS (Section 2.11.5)</td><td>In view of this and the larger proportion of deaths observed for teclistamab ([redacted]% vs. [redacted]% talquetamab) and the generally worse adverse event rate for teclistamab seen in Submission Tables 40 to 49, the EAG consider the Weibull models to represent the most suitable option to model TTD.</td><td>CiC marking amended</td></tr>
<tr><td>Page 136, Section</td><td>The PFS and PPS health</td><td><table>
<tr><th>Health state</th><th>Utility value (SE)</th><th>Source</th></tr>
</table></td><td>CiC marking amended</td></tr>
</table>

3.4.9, Table 33	state utility values and their standard errors require CiC highlighting in alignment with the CS (Section 3.4.5)	PFS [redacted] ([redacted]) — MonumenTAL-1 trial ([redacted] DCO, CS model [lowest AIC]) PPS [redacted] ([redacted]) — MonumenTAL-1 trial ([redacted] DCO, CS model [lowest AIC]) AIC, Akaike information criterion; CS, company submission; DCO, data cutoff; PFS, progression free state; PPS, post-progression state; SE, standard error	
Page 145, Section 3.4.11	The absolute and proportional QALY shortfalls require CiC highlighting in alignment with the CS (Section 3.7)	Based on the calculations the absolute and proportional shortfalls were [redacted] years and [redacted], respectively, which are less than the threshold of 12 years and 0.85; indicating that talquetamab when compared to teclistamab does not meet the severity modifier threshold.	CiC marking amended
Page 151, Section 3.4.12, Table 42	In the row discussing the IVIg parameter the EAG present estimates of the % of patients in each treatment arm alive, based on CS Figure 27 (Section 3.3.2). Given that Figure 27 is	Since the company model shows that by 15 years (CS Figure 27) only about [redacted] of teclistamab arm remain alive compared with [redacted] of talquetamab (Cohort C) arm, the EAG concludes that use of IVIg would be greater for talquetamab arm than for teclistamab arm patients irrespective of any subsequent treatments they may or may not receive.	CiC marking amended

<table>
<tr><td></td><td>CiC, these estimates should also be CiC</td><td></td><td></td></tr>
<tr><td>Page 159, Section 4.2.1, Table 45</td><td>The incremental costs for teclistamab are commercially sensitive so require CiC highlighting, in alignment with the CS (Section 3.10.1)</td><td>[redacted]</td><td>CiC marking amended</td></tr>
<tr><td>Page 159, Section 4.2.1, Table 46</td><td>The incremental costs for teclistamab are commercially sensitive so require CiC highlighting in alignment with the CS (Section 3.10.1)</td><td>[redacted]</td><td>CiC marking amended</td></tr>
<tr><td>Page 173, Section 5.1, Table 49</td><td>The base case INHB does not require CiC highlighting in alignment with</td><td><table><tr><th colspan="4">Talquetamab versus teclistamab</th></tr><tr><th>Inc. Costs (£)</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th><th>INHB (£30,000 per QALY)</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>£29,277</td><td>0.05</td></tr></table></td><td>CiC marking amended</td></tr>
</table>

	the CS (Section 3.10.1)		

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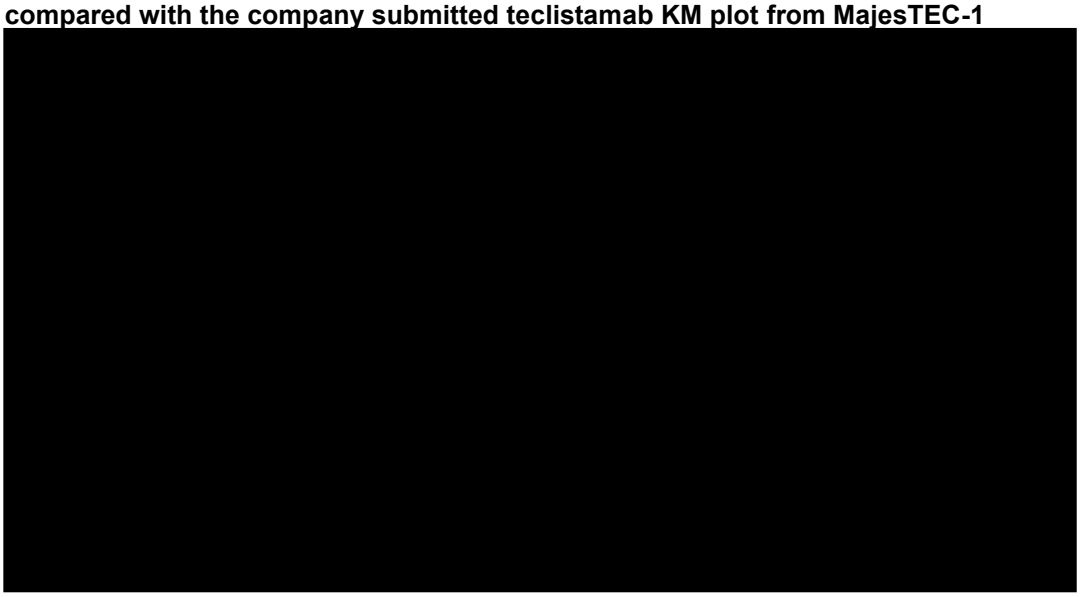
Appendix

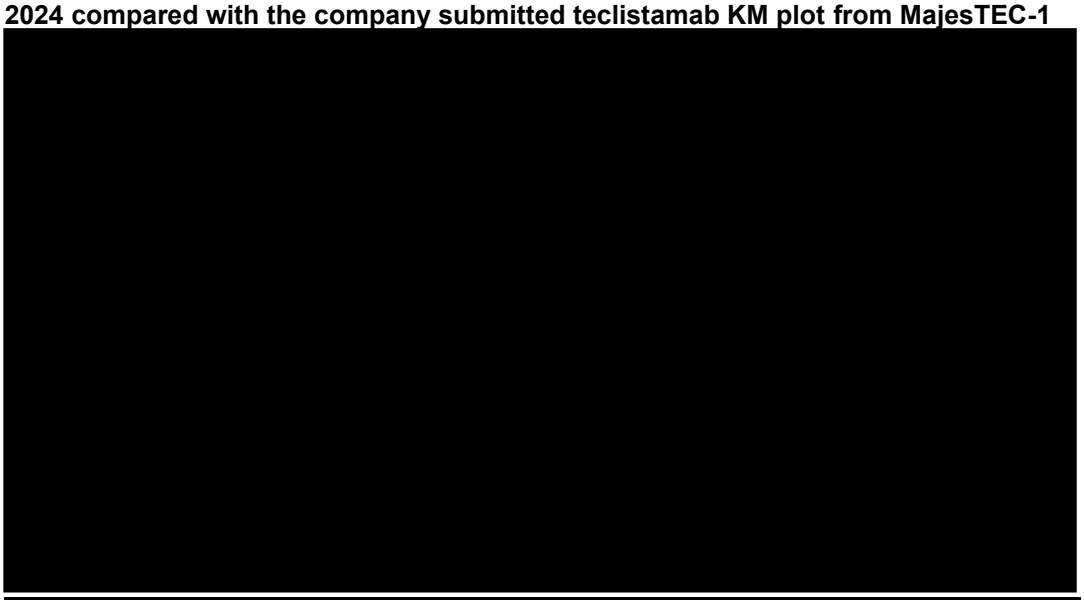
Appendix A: Corrected overlaid OS KM curves for teclistamab

Figure 2. Corrected teclistamab reconstructed OS KM plots (95% CI) from Perrot 2025 compared with the company submitted teclistamab KM plot from MajesTEC-1



Abbreviations: KM: Kaplan-Meier; OS: overall survival.
Source: Perrot, et al. 2025.[11]

Figure 3. Corrected teclistamab reconstructed OS KM plots (95% CI) from Riedhammer 2024 compared with the company submitted teclistamab KM plot from MajesTEC-1



Abbreviations: KM: Kaplan-Meier; OS: overall survival.
Source: Riedhammer, et al. 2024[10]