Single Technology Appraisal

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 (Janssen)
   a. Submission
   b. Submission addendum
   c. Summary of information for patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Blood Cancer UK
   b. Myeloma UK
   c. Royal College of Pathologists
   d. UK Myeloma Society-Royal College of Physicians-Royal College of Pathologists
   e. NHS England

4. **Expert personal perspectives** from:
   a. Dr Rakesh Popat – clinical expert, nominated by Johnson & Johnson Innovative Medicine (Janssen)
   b. Dr Karthik Ramasamy – clinical expert, nominated by the UK Myeloma Society
   c. Caroline Donoghue – patient expert, nominated by Myeloma UK
   d. Kathryn Oddie – patient expert, nominated by Myeloma UK

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
   a. External Assessment Report
   b. EAG addendum to EAR (1)
   c. EAG addendum to EAR (2)
   d. EAG addendum to EAR (3)
   e. EAG critique of company submission addendum

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

Teclistamab for treating relapsed or refractory multiple myeloma after 3 therapies

[ID6333]

Document B

Company evidence submission

5th February 2024

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ID6333_Teclistamab_NICE_Document B_CON	V1.0	Yes	5th February 2024

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Abbreviations

Acronym	Definition
3L	Third-line
4L	Fourth-line
5L	Fifth-line
ACM	Appraisal Committee Meeting
ADC	Antibody Drug Conjugate
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
AMC	Achieved Meaningful Change
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Average Treatment Effect for The Control
ATE	Average Treatment Effect
ATO	Average Treatment Effect for The Overlap Population
ATT	Average Treatment Effect on The Treated Population
BCMA	B-Cell Maturation Antigen
BIC	Bayesian Information Criterion
BMP	Bortezomib, Melphalan and Prednisone
BNF	British National Formulary
Bor	Bortezomib
BSA	Body Surface Area
BSH	British Society for Haematology
CAR	Chimeric Antigen Receptor
CAR-T	Chimeric Antigen Receptor T-Cell
CD38	Cluster of Differentiation 38
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CEM	Cost-Effectiveness Model
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRAB	Calcium levels (hypercalcemia), Renal impairment, Anaemia and Bone disease
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CUA	Cost-Utility Analysis
Dara	Daratumumab
DCO	Data Cut-off

Dex	Dexamethasone
DHSC	Department of Health and Social Care
DLT	Dose-limiting toxicity
DoR	Duration of Response
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EHA	European Haematology Association
Elran	Elranatamab
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EOL	End of Life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire
EOT	End of Treatment
EQ-5D	EuroQol Five Dimensions Five Level Questionnaire
ESMO	European Society for Medical Oncology
FISH	Fluorescence in-situ Hybridisation
FLC	Free Light Chain
GCP	Good Clinical Practice
GHS	Global Health Status
GPM	General-Population Mortality
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ID	Identification
IFN-y	Interferon Gamma
Ig	Immunoglobin
IL	Interleukin
IMiD	Immunomodulatory Agent
IMWG	International Myeloma Working Group
IPD	Individual Patient-Level Data
IPTW	Inverse Probability of Treatment Weighting
IRC	Independent Review Committee
ISS	International Staging System

ITC	Indirect Treatment Comparison
IV	Intravenous(ly)
IVIg	Intravenous Immunoglobulin
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
Len	Lenalidomide
LOT	Line of Treatment
LYG	Life-Years Gained
mAb	Monoclonal Antibody
MAIC	Matching-Adjusted Indirect Treatment Comparison
MHRA	Medicines and Healthcare Products Regulatory Agency
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MyPOS	Myeloma Patient Outcome Scale
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NCRAS	National Cancer Registration and Analysis Service
NCRD	National Cancer Registration Dataset
NE	Not Evaluable
NHB	Net Health Benefit
NHS	National Health Service
NHSE	NHS England
NICE	National Institute of Health and Care Excellence
NR	Not Reported
NRCAS	National Cancer Registration and Analysis Service
ONS	Office for National Statistics
ORR	Overall Response Rate
OS	Overall Survival
Pan	Panobinostat
PAS	Patient Access Scheme
PD	Progressive Disease
PF	Progression-Free
PFS	Progression-Free Survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	Public Health England
PI	Proteasome Inhibitor
Pom	Pomalidomide
PomDex	Pomalidomide plus dexamethasone

PR	Partial Response
PRO	Patient-Reported Outcome
PS	Propensity Score
PSA	Probabilistic Sensitivity Analysis
PSM	Partitioned-Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1W	Once Weekly
Q2W	Once Every Other Week
Q4W	Once Every Four Weeks
QALE	Quality-Adjusted Life Expectancy
QALY	Quality-Adjusted Life Year
QW	Once Weekly
RP2D	Recommended Phase II Dose
RRMM	Relapsed or Refractory Multiple Myeloma
RWE	Real-World Evidence
SACT	Systemic Anti-Cancer Therapy Dataset
SAE	Serious Adverse Event
sATC	Stabilised ATC
SC	Subcutaneous
sCR	Stringent Complete Response
SD	Standard Deviation
SE	Standard Error
SLR	Systematic Literature Review
SMD	Standardised Mean Differences
SMM	Smouldering Multiple Myeloma
SmPC	Summary of Product Characteristics
SoC	Standard of Care
TA	Technology Appraisal
TCE	Triple-Class Exposed
TEAE	Treatment-Emergent Adverse Event
TNF-a	Tumour Necrosis Factor - Alpha
ToT	Time on Treatment
TSD	Technical Support Document
TTD	Time to Treatment Discontinuation
TTNT	Time to Next Treatment
TTR	Time to Response
Tx	Treatment
UK	United Kingdom
ULN	Upper Limit of Normal
USA	United States of America

VAS	Visual Analogue Scale
VGPR	Very Good Partial Response
WTP	Willingness To Pay

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

B.1.1 *Decision problem, description of the technology and clinical care pathway*

This submission covers the full marketing authorisation of teclistamab, 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] Teclistamab is positioned within the scope of its marketing authorisation, which is also in line with the patient population of the MajesTEC-1 clinical trial, the principal clinical evidence base for teclistamab in this indication (see Section B.2.3). An overview of the decision problem addressed in this submission compared to the final scope issued by NICE, is summarised in Table 2.[2]

Triple-class-exposed RRMM emerges after all effective therapies have failed; therefore, patients have an acute and very high unmet medical need. In the absence of therapies specifically licensed for triple-class-exposed RRMM, clinical experts confirmed that they face the prospect to treat patients with previously trialled drug classes, of which the most predominantly used is pomalidomide plus low-dose dexamethasone (PomDex). They estimated that 90% of patients would receive PomDex at this stage, making PomDex the only relevant comparator to teclistamab in this indication.

The estimation from clinical experts is supported by the findings from real-world data from a Janssen-sponsored study conducted in England in patients with TCE RRMM using National Cancer Registration and Analysis Service (NCRAS) data, hereafter referred to as the **UK RW TCE Cohort Study.** In this study, over 63% of patients with TCE RRMM received a pomalidomide-based regimen.[3-7]

Both the clinical advice and real-world evidence position PomDex as the only relevant comparator to teclistamab in this submission. This consideration is also aligned with the recent conclusions of the NICE appraisal committees in TA658, TA783 and TA889 on the appropriate comparators at this stage in therapy.[4, 8, 9]

All other treatments specified in the NICE final scope are either used earlier in the treatment pathway in UK clinical practice, are subject to ongoing NICE evaluations and thus are not considered routine practice, or are no longer being used due to safer, more effective treatments being introduced. Additionally, clinicians do not routinely re-challenge TCE RRMM patients with the same treatments if patients had progressed on those in previous therapy lines, and therefore these treatments are used in different patient groups to those eligible for teclistamab.

Further rationale for excluding any comparators from the evidence submission is provided in Table 1 below.

Table 1: Summary of the comparators included in the final NICE scope and justification of their relevance

Treatment	Relevant Comparator	Justification
Relevant Comparator		
Pomalidomide plus low-dose dexamethasone (PomDex)	Yes	Feedback received from UK clinical experts indicated that after three prior therapies, 90% of TCE patients in UK clinical practice receive PomDex, indicating PomDex is the only relevant comparator.[10] Real-world data from the UK RWE TCE study also demonstrated after the main drug classes used to treat MM have been trialled, the most predominantly used therapy (63%) is a pomalidomide-based regimen. PomDex representing the only relevant comparator in this setting is in line with the conclusions of the NICE appraisal committees in TA658,[4] TA783,[8] and TA889[5] on the appropriate comparators for treatment after three prior therapies.[11]
Other Treatments		
Isatuximab plus pomalidomide and dexamethasone (IsaPomDex) *[Subject to NICE evaluation]*	No	*IsaPomDex is not established in routine practice* IsaPomDex is currently available on the Cancer Drugs Fund (CDF) and; although a CDF review is currently underway, the technology is not routinely commissioned at the time of submission for the present appraisal. Therefore, IsaPomDex should not be included as a comparator. The exclusion of IsaPomDex as a relevant comparator is consistent with other ongoing appraisal(s) e.g. ID4026.[12] *IsaPomDex is primarily used in anti-CD38 naïve patients in UK clinical practice* Should IsaPomDex be recommended for routine commissioning during the teclistamab appraisal process, it would still not represent a relevant comparator. To be eligible for teclistamab, patients must have been previously exposed to an anti-CD38 mAb – daratumumab is the only anti-CD38 mAb routinely reimbursed in UK clinical practice.[1] Results from a recently published UK RWE study support this view, where it was highlighted that 95% of patients receiving IsaPomDex are anti-CD38 naïve and therefore would be ineligible to receive teclistamab in UK clinical practice.[13] *Most TCE RRMM patients will be refractory to anti-CD38 mAb at 4L and not eligible for IsaPomDex* Any patients who receive DaraBorDex as a second-line therapy, or DaraLenDex as a first-line therapy, would become refractory to daratumumab (as these treatments given until disease progression) and therefore would be ineligible to receive IsaPomDex. To be eligible to receive IsaPomDex patients must not be refractory to an anti-CD38 mAb.[14] The only patients eligible to receive either teclistamab or IsaPomDex after three prior therapies would need to follow a very specific treatment pathway, where they receive prior daratumumab without becoming refractory to it. This would mean that they would need to be stem cell

		transplant (SCT)-eligible and receive first-line treatment with DaraBorThalDex (the only reimbursed daratumumab-regimen in the UK where daratumumab is not given until disease progression), before then receiving a non-daratumumab based regimen in the second-line setting (likely either CarDex or CarLenDex).[15] In particular, given the prevalence of DaraBorDex as a second-line treatment option for patients with RRMM, only a very small proportion of patients would be anticipated to follow a treatment pathway whereby they become TCE without becoming daratumumab-refractory (with these numbers anticipated to reduce further as the treatment pathway for earlier lines of therapy evolves). All the above lead to the conclusion that IsaPomDex is not a relevant comparator to teclistamab in this submission.
Elranatamab *[Subject to NICE evaluation]*	No	At the time of this submission, elranatamab has not received a positive recommendation by NICE and is not routinely used in UK clinical practice. As such, elranatamab does not represent a relevant comparator to teclistamab at this time. This is in line with the ongoing NICE appraisal for IsaPomDex, where elranatamab was not considered a relevant comparator[4].
Lenalidomide plus dexamethasone (LenDex)	No	LenDex is recommended as a first-line (TA587),[16] second-line (TA586)[17] and third-line (TA171)[18] treatment option in UK clinical practice, as well as in combination with daratumumab (TA917) as a first-line treatment option, [19] and ixazomib (TA870) after 2 or 3 prior lines of therapy.[20] After three prior therapies, patients with TCE RRMM are therefore highly likely to already received LenDex. UK clinical experts consulted as part of TA505[21] and ID4026[12] highlighted that LenDex is predominantly used in the third-line setting, if not previously received at first line. Due to the pathophysiology of MM, patients develop resistance to therapies after they have been exposed to them for extended amounts of time, therefore the recycling of therapies or classes of agents has limited efficacy in these patients. As such, given this combination would most likely be used earlier in the pathway, the re-use in this setting would be limited by previous exposure at earlier lines in the pathway. Therefore, LenDex does not represent a relevant comparator to teclistamab for patients having received three prior therapies.
Panobinostat plus bortezomib and dexamethasone (PanBorDex)	No	PanBorDex was historically used in patients with RRMM after three prior therapies, but is no longer used due to ongoing toxicity concerns. This was supported by clinical experts in TA658,[4] TA783[4, 8] and as part of an ACD for TA10568 (belantamab mafodotin) where clinicians stated that *"PanBorDex is rarely used in clinical practice*".[22] In light of these insights from clinicians, the committees in TA658, TA783 and ID2701 concluded that PanBorDex is not used in patients who have received three prior therapies.[4, 8, 22] NICE also removed PanBorDex as a relevant comparator in patients who have received three prior therapies from the final scope of the ongoing CDF review of IsaPomDex (ID4067)[5], due to the Committee's conclusion in TA658,[4]

		as well as comments received during the consultation. As such, PanBorDex is not a relevant comparator for teclistamab.
Daratumumab monotherapy	No	Owing to the recent positive recommendations of DaraLenDex in the front line (TA917)[19] and DaraBorDex in the second-line setting (TA897),[23] daratumumab monotherapy is now rarely used in patients who have received three prior therapies as clinicians prioritise the use of daratumumab as early as possible in the treatment pathway. Furthermore, daratumumab represents the only reimbursed anti-CD38 mAb in UK clinical practice, and by definition, patients must have received prior daratumumab to be eligible for treatment with teclistamab. However to receive daratumumab monotherapy, patients must not be previously refractory to daratumumab treatment – as previously detailed for IsaPomDex, the proportion of patients who are exposed but not refractory to prior daratumumab is likely to be extremely low.[15] As such, daratumumab monotherapy is not a relevant comparator for TCE patients, who have already been exposed to an anti-CD38 mAb.
Ixazomib plus lenalidomide and dexamethasone (IxaLenDex)	No	For the reasons previously detailed for LenDex, IxaLenDex does not represent an appropriate comparator to teclistamab after three prior therapies, as this patient population would likely have already received LenDex and patients are not routinely re-challenged with the same agents in later lines of therapy. The exclusion of IxaLenDex as a relevant comparator in TCE patients in the fourth-line setting was supported by feedback received from clinical experts consulted during the Committee meeting for the CDF exit review of IsaPomDex, who confirmed that IxaLenDex is not used in this setting in UK clinical practice. The exclusion of IxaLenDex as a comparator to IsaPomDex in this setting was accepted by the Committee [ID4067].
Cyclophosphamide plus dexamethasone (CycloDex)	No	Cyclophosphamide plus dexamethasone (or an alternative alkylating chemotherapy) is not standard of care for patients who have received three prior therapies, and as such this treatment is not a relevant comparator. Clinical insights received by Janssen have indicated that this chemotherapy combination would be used as a third-line treatment option, or as a salvage option at fifth line and beyond for palliative care where it would be typically used in combination with a PI, such as bortezomib. The limited use of CycloDex was also noted in the UK RWE TCE study, where no patients were reported to receive CycloDex as a fourth line treatment[24].

Abbreviations: Bor: bortezomib; CDF: Cancer drugs fund; Cyclo: cyclophosphamide; Dara: daratumumab; Dex: dexamethasone; Elran: elranatamab; Isa: Isatuximab; Ixa: Ixazomib: Len: Lenalidomide; mAb: monoclonal antibody; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National institute for Health and Care Excellence; Pan: 15satuximab15t; PI: proteasome inhibitors; Pom: pomalidomide; RRMM: relapsed/ refractory multiple myeloma; TCE: triple class exposed; UK: United Kingdom.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed or refractory multiple myeloma after 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 treatment	Adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy	N/A
Intervention	Teclistamab	Teclistamab	N/A
Comparator(s)	• Lenalidomide plus dexamethasone • Panobinostat plus bortezomib and dexamethasone • Pomalidomide plus low-dose dexamethasone • Daratumumab monotherapy • Ixazomib plus lenalidomide and dexamethasone • Cyclophosphamide plus dexamethasone • Isatuximab plus pomalidomide and dexamethasone (subject to NICE evaluation) • Elranatamab (subject to NICE evaluation)	Pomalidomide plus low-dose dexamethasone (PomDex)	The rationale for including PomDex as the only relevant comparator to teclistamab in this submission is provided in Table 1 above
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects (Aes) of	Outcomes included in the submission are: • Overall survival (OS) • Progression-free survival (PFS)	N/A

	treatment • Health-related quality-of-life (HRQoL)	**Response rates:** • Overall response rate (ORR) • Duration of response (DoR) • Rate of very good partial response or better (≥VGPR) • Rate of complete response (CR) or better • Rate of stringent complete response (sCR) • Rate of partial response (PR) • Rate of minimal response (MR) • Rate of stable disease (SD) • Rate of progressed disease (PD) **Other outcomes:** • Adverse events (AEs) • Time to treatment discontinuation (TTD) • Time to next treatment (TTNT) • Minimal residual disease (MRD) negativity rate • Health-related quality of life (HRQoL)	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE	The economic analysis aligns with that described in the NICE decision problem	NA

	technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		

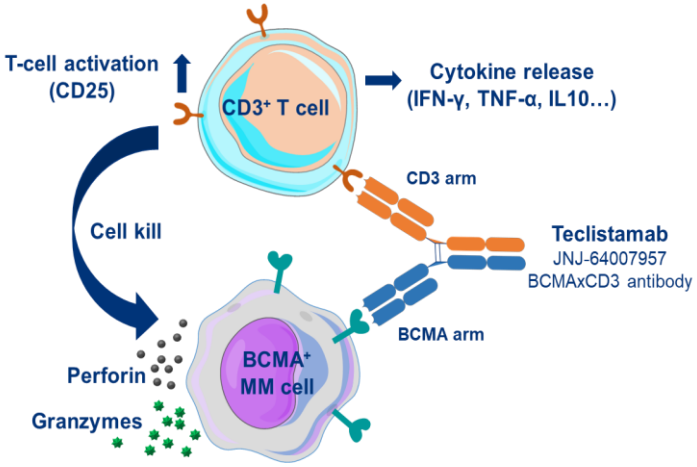
Abbreviations: Aes: adverse events; CR: complete response; DOR: duration of response; HRQoL: health related quality-of-life; MR: minimal response; MRD: minimal residual disease; NHS: National Health Service; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PomDex: Pomalidomide plus low-dose dexamethasone; PR: partial response; Scr: stringent complete response; TTD: time to treatment discontinuation.

B.1.2 *Description of the technology being evaluated*

The summary of product characteristics (SmPC) and UK public assessment report (PAR) for teclistamab in the indication of relevance to this submission are provided in the reference pack accompanying this submission (see Appendix C).

A description of the technology being appraised, teclistamab, is presented in Table 3.

Table 3: Technology being appraised

UK approved name and brand name	Teclistamab (Tecvayli®)
Mechanism of action	Teclistamab is a first-in-class, humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody that binds to the B cell maturation antigen (BCMA) present on the surface of malignant MM cancer cells and CD3 receptors expressed on the surface of T cells of the immune system. With its dual binding sites, teclistamab is able to draw CD3+ T cells in close proximity to BCMA+ cells, allowing the patient's own immune system to destroy the MM cancer cells.[1] **Figure 1:** Mechanism of Action of Teclistamab  **Abbreviations:** BCMA: B-cell maturation antigen **Source:** Adapted from: Ben-Ari (2022).[25] Based on *in vitro* studies, the binding of teclistamab to both CD3-expressing T cells and BCMA+ cells induces T cell mediated cytotoxicity through the recruitment of CD3-expressing T cells to the BCMA expressing cells. This then mediates T-cell activation and the subsequent target cell lysis of BCMA-expressing myeloma cells.[26]
Marketing authorisation/CE mark status	In August 2022, the European Medicines Agency (EMA) granted marketing authorisation to teclistamab.[27, 28] A UK licence for teclistamab was granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 9th November 2022, following the European Commission (EC) Decision Reliance Procedure.

Indications and any restriction(s) as described in the SmPC	The licensed indication for teclistamab is:[27] *"As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy"*
Method of administration and dosage	Teclistamab is available as a 10mg/ml or 90mg/ml solution for SC injection.[27] The recommended doses of teclistamab are 1.5 mg/kg by SC injection weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg at day 1 and day 3 respectively.[29] Patients who achieve complete response or better for a minimum of six months may receive a biweekly treatment schedule, with the option to reduce dosing frequency to 1.5 mg/kg every two weeks. Details of the full dosing schedule for teclistamab are provided in the SmPC.[27] Drug administration should be carried out by a healthcare professional with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome.[27] Treatment should be continued until disease progression or unacceptable toxicity.[27]
Additional tests or investigations	Due to the risk of cytokine release syndrome, patients are instructed to remain within proximity of a healthcare facility, and monitored for signs and symptoms daily for 48 hours after administration of all doses within the teclistamab step-up dosing schedule.[27] Prior to starting treatment with teclistamab, antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation, per local institutional guidelines.[27]
List price and average cost of a course of treatment	The list price for available formulations of teclistamab are provided below: • Teclistamab 90 mg/ml solution: £3,952.78 per vial • Teclistamab 10 mg/ml solution: £775.14 per vial
Patient access scheme (if applicable)	This submission includes a confidential simple patient access scheme (PAS) for teclistamab, representing a discount to the list price of [redacted] The resulting price of teclistamab with PAS is: • Teclistamab 90 mg/ml solution: [redacted] per vial • Teclistamab 10 mg/ml solution: [redacted] per vial

Abbreviations: BCMA: B cell maturation antigen; IgG4- PAA: immunoglobulin G4-proline, alanine, alanine; MHRA: Medicines and Healthcare Products Regulatory Agency; MM: multiple myeloma; PAS: patient access scheme; SC: subcutaneous; SmPC: summary of product characteristics.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Triple-class-exposed relapsed/refractory multiple myeloma (TCE RRMM) emerges after all effective therapies have failed; therefore, patients experience substantial disease-related burden

- MM is a rare and incurable haematological cancer accounting for 2% of all new cancer cases in England and is associated with high clinical burden, with patients often presenting with recurring or persistent infection, fatigue and unremitting bone pain[30, 31]
- All patients will eventually relapse or fail to respond to each line of treatment, as MM progresses to relapsed/refractory MM (RRMM).[32] Once patients have received treatment with a proteasome inhibitor (PI), immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody (mAb), this is classed 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[33, 34]
- Patients with TCE RRMM experience worsening treatment responses (e.g., duration and depth), faster disease progression, and poorer survival outcomes when compared with patients having received fewer lines of therapy.[35, 36] This is due to patients becoming refractory to available treatments, and the dearth of novel treatments for this patient population in the UK

As they near the end of their terminal illness, triple-class exposed RRMM patients have an acute and very high unmet medical need for a treatment option with a novel mechanism of action to drive deep and durable response.

- After the main drug classes used to treat MM have been trialled, treatment options are limited, and patients face the prospect of receiving salvage therapy with previously trialled regimens.
- PomDex appears to be the predominant treatment option in TCE RRMM. The results from a real-world retrospective cohort study using data from the UK-based NCRAS dataset (Section B.2.9) showed that TCE RRMM patients receiving PomDex are nearing the end of their terminal illness with a median life expectancy of 9.78 months (95% CI: 8.64, 10.82 months).[24]
- Such findings underscore the urgent unmet medical need for innovative treatment options with a novel mechanism of action to be made available to TCE RRMM patients, who reach the end of the pathway with a disease resistant to mainstream treatments.
- With the recent introduction of DaraLenDex and DaraBorDex, the number of patients with TCE RRMM will inevitably increase over time.
- Hope and treatment choice are critical to UK myeloma patients and those around them, even more so after 3 prior therapies and beyond.[37] Given the recent access setbacks in this setting, RRMM patients expressed serious concerns about running out of effective therapies in the NHS.

With its innovative mechanism of action, teclistamab represents a step-change in the management of MM as an effective steroid-free monotherapy specifically for patients with TCE RRMM

- Teclistamab is a first-in-class, bispecific antibody conjugate which binds to B-cell maturation antigens (BCMA) on MM cells and CD3 receptors on the T-cells of the immune system, stimulating the patient's own immune system to destroy cancerous MM cells[1]
- This innovative mode of action would introduce a novel class of MM treatment in the UK – the first since the introduction of anti-CD38 mAbs over 5 years ago[38]

- Teclistamab is positioned within the scope of its marketing authorisation: "*As a monotherapy for treatment of RRMM adult patients 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 received*"[1]
- UK clinicians indicated that, owing to the extremely poor survival outcomes in triple-class exposed RRMM, teclistamab would be used as early as possible in the treatment pathway. Therefore, it is proposed to position teclistamab alongside PomDex for RRMM patients who have received three prior lines of therapy.
- By driving deep and durable responses in a disease resistant to mainstream treatments, teclistamab would address the current unmet medical need for an effective novel treatment option which can better control disease for TCE RRMM patients and ultimately lead to improvements in patient HRQoL and prolonged survival (Section B.2).
- Teclistamab has already garnered positive recommendations across Europe[28, 39]. Its inclusion in the UK's MM treatment pathway is crucial for maintaining the country's leadership in myeloma innovation. By consistently providing MM patients with cutting-edge therapies to enhance their health condition and priming the pathway for upcoming novel agents (such as XPO1, BCL-2, GPRC5D and FcRH5 targets), the UK will remain at the forefront of myeloma care.

B.1.3.1 Disease overview

Presentation

MM is a rare and 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.[40-42] 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 **c**alcium levels (hypercalcemia), **r**enal impairment, **a**naemia and **b**one disease (CRAB).[40, 43]

Patients with MM experience symptoms like fatigue, bone pain, recurrent or persistent infection and hyperviscosity, all of which significantly impacting their health-related quality of life (HRQoL) on a daily basis.[40, 43, 44]

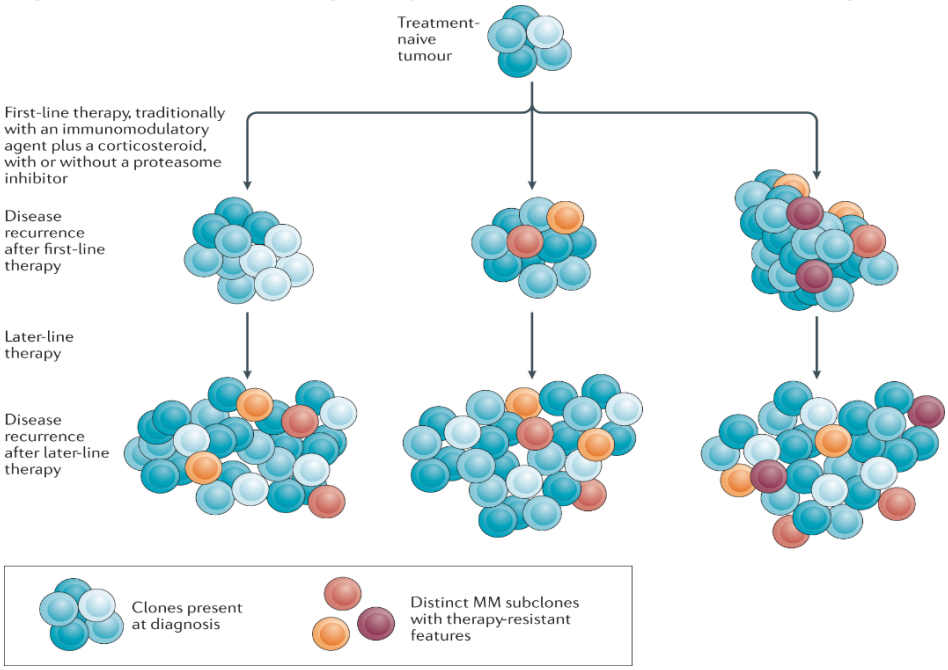
Heterogeneity

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.[45] 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.[46-48] 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.[49] Unfortunately, each subsequent relapse carries a higher risk of additional clones arising due to genetic mutations within the myeloma cells.[50] Nearly all patients will experience disease relapse and become refractory to at least one

class of drugs commonly used for MM treatment.[51] Understanding this genetic complexity is crucial for tailoring effective therapies and improving outcomes for MM patients.

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



Abbreviations: MM: multiple myeloma.
Source: Mikkilineni and Kochenderfer (2021)[52]

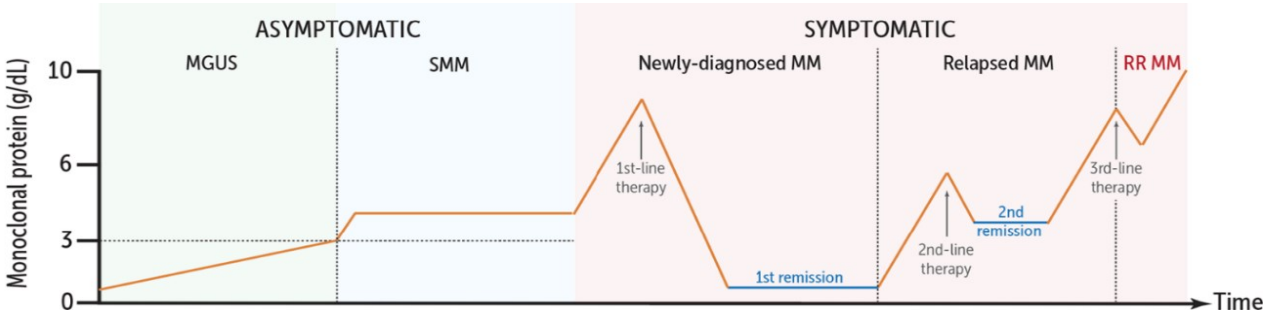
Treatment challenges

The emergence of novel therapeutic agents has significantly enhanced survival rates and HRQoL for patients with MM. Despite these advances, MM remains a predominantly incurable malignancy, and nearly all patients eventually experience relapse or fail to respond to treatment, becoming refractory to available options.[32]

The clinical journey MM and progression to RRMM - from its asymptomatic precursors (monoclonal gammopathy of undetermined significance [MGUS] and smouldering MM [SMM]) as outlined by the International Myeloma Working Group (IMWG) criteria - is illustrated in Figure 3.[53] RRMM is characterised by non-responsiveness during on salvage therapy or progression within 60 days of last therapy, even in patients who achieved minimal response (MR) or better previously.[54-56]

While new treatments have extended life expectancy, patients previously exposed to an IMiD, a PI, and an anti-CD38 mAb face limited options when they have progressed on their last therapy – referred to as triple-class exposed (TCE) RRMM. Understanding these complexities is vital for tailoring effective strategies and advancing MM care.

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).[57]

Prognosis

There are limited data on triple-class-exposed RRMM, although the existing data point towards particularly poor prognosis and a high unmet need for effective therapies. In a UK real-world retrospective cohort study – referred to as the UK RW TCE cohort study – researchers delved into the treatment patterns and clinical outcomes of TCE RRMM patients using NCRAS data.

Within this patient group, the predominant treatment regimen used was PomDex (63% of which 85% received it as their first therapy following triple-class exposure). The study reveals a median overall survival (OS) as low as 9.78 months among patients receiving PomDex in UK clinical practice (N=645; 95% CI: 8.64, 10.82 months).[24] Further details of the UK RW TCE cohort study are outlined in Section B.2.9 and a comprehensive discussion of OS and progression-free survival (PFS) outcomes in this challenging patient population is presented in Section B.1.3.3.

B.1.3.2 Epidemiology

In 2017, England witnessed 5,034 new cases of MM, accounting for 2% of all new cancer cases.[30] Over the last decade, MM incidence rates have risen by approximately 15%. A study projects an additional 11% increase between 2014 and 2035, primarily reflecting changes in risk factors and diagnostic improvements.[30]

Several factors are associated with an increased risk of developing MM: [58]

- Age: MM most commonly affect individuals over the age of 60
- Race: Black people experience MM at twice the frequency of white people, although the reasons for this disparity remain unclear
- 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
- Sex: MM is more prevalent in men (with an incidence of 55% in males compared to 45% in females)

As noted in Section B.1.3.1 above, despite advances in treatment, MM remains 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.[30]

Epidemiological data on patients with TCE RRMM is scarce. This limitation arises from the rare nature of the condition, affecting approximately 4 in 10,000 persons in the European Union as indicated in the initial orphan designation for teclistamab (EU/3/20/2331).[59]

A German study using the Oncology Information Service registry reported that 12% (n=411) of the 3,384 evaluated RRMM patients were TCE.[60] In the UK, the UK RW TCE cohort study initially identified 366 patients diagnosed with TCE RRMM in England between 2013 and 2019.[11] Following an extension of the study period for a median follow-up period of 23.0 months, the study identified a total of 1,422 patients with TCE RRMM.[24]

In the budget impact model designed for this submission, an approximate projection indicates that around [redacted] patients would receive a diagnosis of TCE RRMM and commence 4L treatment annually. However, with the recent positive recommendations for DaraLenDex and DaraBorDex in earlier lines of therapy, the size of the TCE patient cohort in the UK is expected to continue growing over time.

B.1.3.3 Burden of TCE RRMM and impact on patients and carers

Disease presentation

MM imposes a significant clinical burden on patients. Commonly, patients present with recurring or persistent infections, fatigue and unrelenting bone pain.[31] 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.[61] Furthermore, more than two thirds of all MM patients experience anaemia due to disease-related complications.[62]

As MM progresses to RRMM, the disease burden intensifies. Patients with relapsed/progressive disease report more severe and numerous symptoms compared to those with newly diagnosed or stable MM.[33] The progressive disease symptoms and treatment-associated complications include weakness, fatigue, bone pain, weight loss, confusion, excessive thirst and constipation.[63]

A 2020 cross-sectional, multicentre study in MM patients demonstrated that patients with RRMM had a higher Myeloma Patient Outcome Scale (MyPOS) score than those with newly diagnosed or stable MM. This underscores the substantial disease burden faced by RRMM patients.[64]

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 detriments their quality of life. A diagnosis of MM has a profound psychological impact, with patients experiencing fear due to the unpredictability of the disease. Some even describe their diagnosis as a ticking ‘time bomb’, living in constant fear of a relapse.[65] The uncertainty about the future causes ongoing anxiety

and affects patients' relationships with family and friends who often act as informal caregivers.[66, 67]

Initial relapses in the disease are associated with a period of negative emotions, including hopelessness and resignation.[66] Subsequent relapses are linked to increasing distress and pessimism.[66] This becomes especially critical when patients feel that the primary available treatment options have been exhausted, as is the case for patients with triple-class exposed RRMM.[66] The continued uncertainty surrounding MM 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.[34] Additionally, depression affects one in four MM patients.[68]

Furthermore, HRQoL significantly deteriorates with each relapse and subsequent line of treatment (LOT). In a French study of symptomatic MM patients, EORTC QLQ-MY20 scores were significantly worse for those receiving later treatment lines and supportive care, showing significant decreases in HRQoL with each successive LOT ($p<0.0001$). This decline affects well-being related to future perspective, body image, disease symptoms, and treatment side effects.[69] Similar findings were observed in the LocoMMotion study where HRQoL worsened with each subsequent treatment. These patients (n=99) reported worse global health status, physical functioning, and symptoms of pain and fatigue compared to baseline.[70] This evidence highlights the substantial impact on HRQoL for MM patients with advanced and heavily treated disease, emphasising the need for comprehensive support throughout their journey.

Above all, due to the poor prognosis, 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.[33, 71, 72] An indirect comparison of HRQoL scores using the European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Global Health Status (GHS) and EuroQol Five Dimensions Five Level Questionnaire (EQ-5D) across different advanced cancers revealed that RRMM has a similar or potentially greater impairment on HRQoL than other advanced cancers.[73]

The emotional toll of this disease and the impact on HRQoL are significant and require comprehensive support for patients and their caregivers.

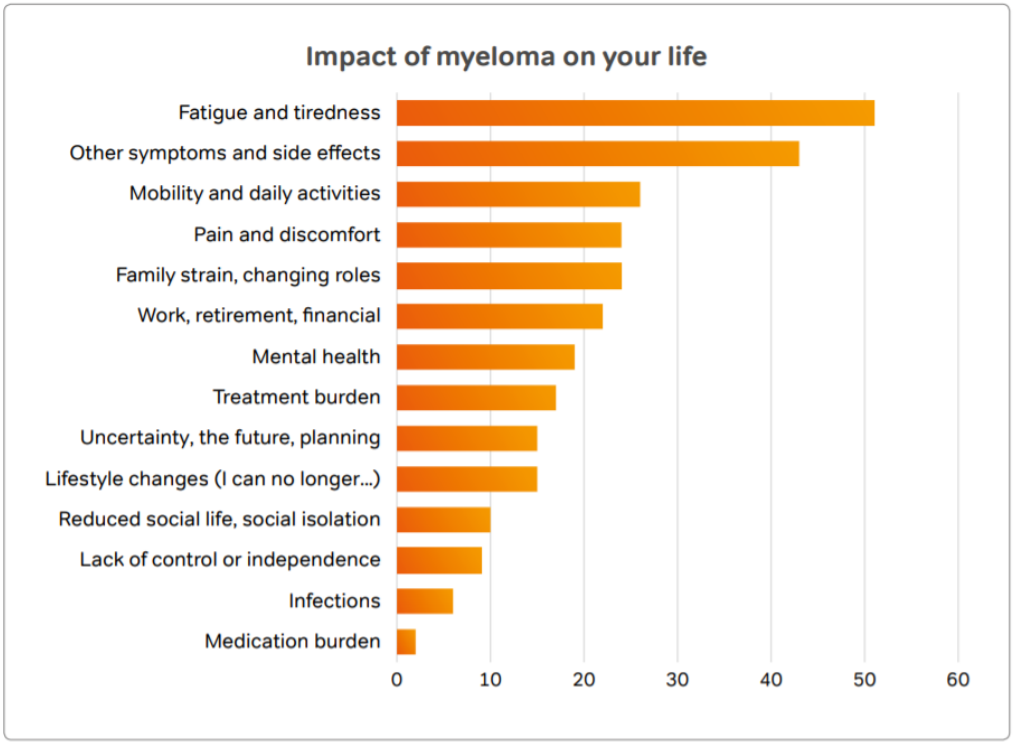
MM patient preferences

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). NICE's conclusion was: there is 'a *clear scope for better use of quantitative patient preferences studies within HTA*'.[74] The study employed robust research methodology, including a nested survey and a focus group involving 97 MM patients. The goal was to gain deeper insights into the patient experience and the types of preferences that matter most to them. The key findings are presented below:

- Impact of myeloma: respondents reported that 'Fatigue and tiredness' had the most impact on their lives (Figure 4 below). Additionally, MM affected their personal life by reducing their sense of control/independence, altering their lifestyles, and causing financial strain. These experiences might not be effectively captured in traditional HRQoL instruments.

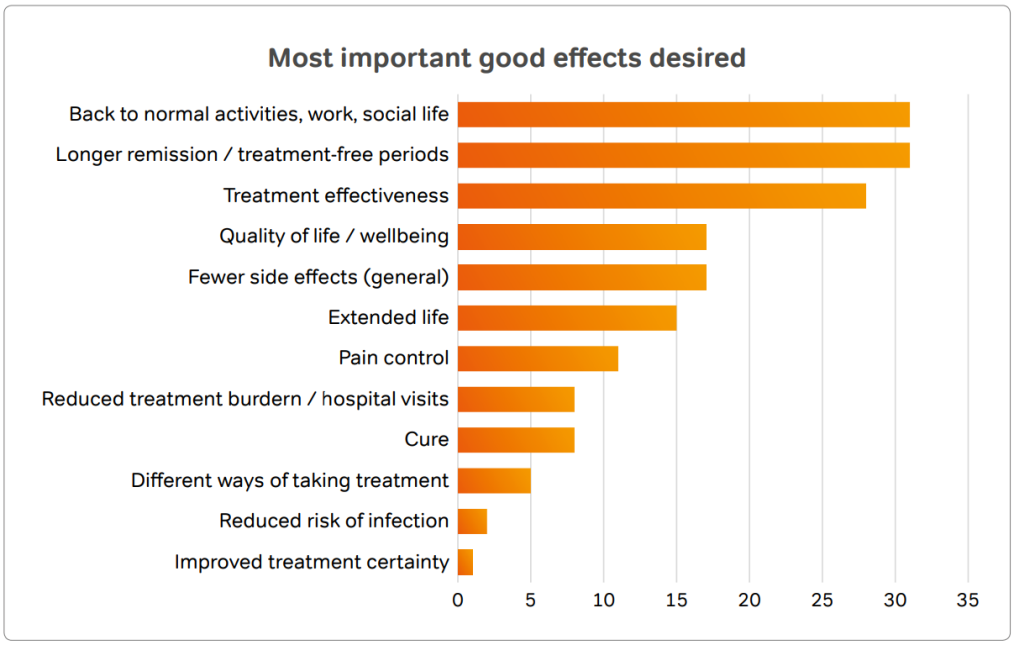
- Treatment preferences: respondents expressed a strong preference for treatments that effectively control the disease (Figure 5 below). The second most important attribute was 'longer remission/treatment-free periods'. Given the finite number of available treatment options and the time-limited effectiveness associated with each of them, patients face poor prognosis of survival. Without new treatments, their ability to be effectively treated for myeloma is constrained. Interestingly, another qualitative research has highlighted the benefits of being treatment-free in MM, emphasizing the need for innovative therapies to extend remission periods and improve patients' quality of life.[75]

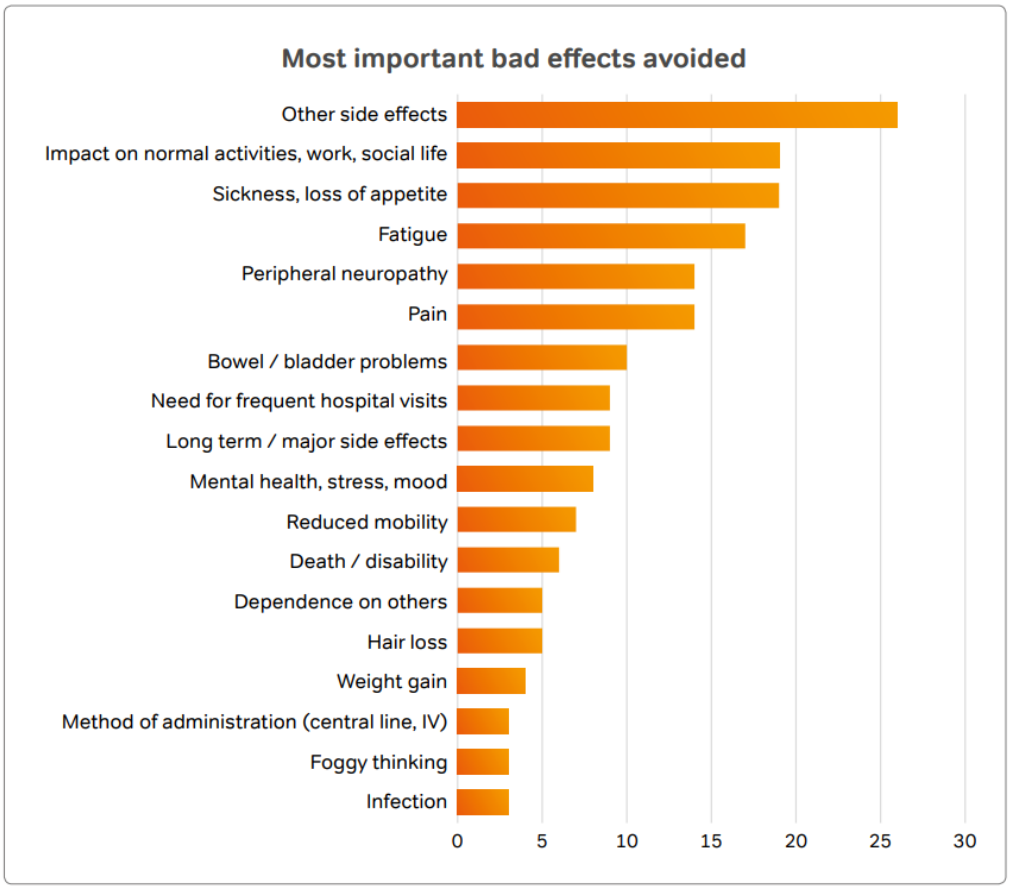
Figure 4: Impact of MM on lives of patients



Abbreviations : MM, multiple myeloma.
Source: Myeloma UK (2019)[76]

Figure 5: Most important good effects desired and most important bad effects avoided by patients with MM





Abbreviations : MM, multiple myeloma.
Source: Myeloma UK (2019)[77]

TCE RRMM patients

Patients with triple-class exposed RRMM experience poor clinical outcomes that deteriorate progressively with each subsequent line of treatment. Unfortunately, the lack of novel treatment options contributes to this decline.

In a US real-world registry study also reported that median OS decreased from 14.1 months (95% CI: 9.4, 19.8) in patients receiving third line treatment, to 7.8 months (95% CI: 5.1, 12.4) in RRMM patients receiving fourth-line treatment and beyond.[78]

Recently, the LocoMMotion real-world prospective study investigated treatment patterns and outcomes in RRMM patients who had undergone at least three prior therapies.[79] The study spanned 86 sites across Europe (including the UK) and the United States. It revealed a lack of a clear standard of care for TCE RRMM patients, with these patients receiving a staggering 92 different combinations of treatments. Patients receiving current treatments experienced poor survival outcomes: the median PFS was 4.6 months (95% CI: 3.9, 5.6), and the median OS was 12.4 months (95% CI: 10.3, NE).[79]

To ensure outcomes pertaining specifically to NHS patients were captured in this submission, a UK-specific real-world cohort study was conducted by Janssen using data from NHS England's (NHSE) cancer and linked datasets (see Section B.2.9). In this study, TCE RRMM patients receiving PomDex had a median OS of 9.78 months (N=645; 95% CI: 8.64, 10.82 months) and the median PFS (using time-to-next treatment [TTNT] as a proxy) was 7.03 months (95% CI: 6.54, 7.81).[24]

In the context of RRMM, treatment objectives extend beyond traditional endpoints such as PFS and OS. A growing body of evidence underscores the significance of achieving depth and sustained response to therapy.[80-82] In a systematic literature review (SLR) analysing 65 RRMM clinical trials, Daniele *et al.* (2023) reported a statistically significant correlation between OS and depth and duration of response. Specifically, the study estimated that 10% increase in ORR, CR and DOR predict incremental median OS gain of 4.6, 11.7 and 14.1 months, respectively.[80] UK clinical experts echoed the importance of achieving durable responses in order to obtain prolonged survival.[83] Furthermore, a separate SLR explored the relationship between HRQoL and clinical response and concluded that deeper treatment responses were associated with improved HRQoL in patients with MM.[84]

The importance of response depth and duration underscores the challenging outcomes associated with current treatments for patients with triple-class exposed relapsed/refractory multiple myeloma. While not specifically conducted in a TCE population, the registrational trial for PomDex (MM-003) trial for PomDex in RRMM patients reported an ORR of 32%. However, only 7% of patients achieved a very good partial response (VGPR) or greater.[85] Among responders, the median duration of response (DOR) was 7.5 months.[85] Similarly, the LocoMMotion study reported an ORR of 29.8% (95% CI: 24.2, 36.0) with a median DOR of 7.4 months for patients receiving 92 unique SoC treatment regimens. Remarkably, only one patient (0.4%) achieved a complete response (CR) or better; while 12.1% of patients achieved a VGPR.[79]

In summary, in patients with multiple myeloma, particularly those with triple-class exposed relapsed/refractory MM, the HRQoL, treatment response and survival outcomes remain

distressingly poor. As the disease progresses and patients experience successive relapses and treatment lines, the burden of MM worsens, impacting both prognosis and well-being. The lack of effective treatments is a source of anxiety for RRMM patients, as well as their caregivers and families. Comments submitted by Myeloma UK during previous appraisals highlighted the serious implications of exhausting treatment options[37]. Addressing the challenges faced by RRMM patients necessitates therapeutic approaches with innovative mechanisms of action that can achieve deep and durable response to enhance both clinical outcomes and patient well-being.

Effect on carers

Most of the clinical management of MM is provided in the outpatient setting; therefore, the bulk of care is informal and provided by partners or family members. A 2016 study carried out by Myeloma UK surveyed 374 carers of patients with MM and found that 71% were caring for a spouse or partner and 23% were caring for a parent.[86, 87] Carers may perform complicated technical procedures (e.g. dressing changes, intravenous line care and injections), assist the patient with daily living, attend appointments and take in complex information.[86] Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their carers.[68]

The informal 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.[88, 89] In a study carried out amongst 118 caregivers of patients with MM, negative associations between HRQoL and burden, information needs, financial needs, emotional needs, and psychological morbidity were found.[90] Additionally, the 2016 Myeloma UK study reported that 98% of carers provide emotional support to their relative or friend with MM and that 94% are emotionally impacted by providing informal care, with the uncertainty of the disease highlighted as a major factor.[91] A cross-sectional survey carried out in four hospitals in the UK also found that almost half (49%; n=132) of the partners of patients with MM report symptoms of anxiety and 14% report symptoms of depression.[68]

A targeted literature review was carried out by Janssen in 2023 to describe the quantitative impact of caregiving on the HRQoL of carers of patients with MM and reported that caregivers often experience reduced HRQoL due to increased stress levels, reduced productivity and financial strain.[87] There is currently a lack of studies reporting carer HRQoL data in specifically TCE RRMM patients, however, it is anticipated that the burden on carers in this setting would be particularly high given the lack of novel treatment options remaining and the worsening physical symptoms of the disease.[31]

Caregivers can suffer financial difficulties as a result of a relative being diagnosed with MM; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.[86] In addition, one study analysing results from an economic questionnaire from patients in a Phase II, multi-centre, international RCT (N=307), including sites in the UK, found that MM causes productivity losses, with carers losing on average 104.5 working hours per year due to providing informal care.[92] Results from the 2016 Myeloma UK study also indicated that 25% of carers were unable to work or had to retire early in order to care for the patient with MM.[91] This economic burden is likely to be particularly high in patients with TCE RRMM.

Overall, the unmet need in supportive care is considerable and carers of patients with TCE RRMM would experience a worsening burden due to the increased care that is associated with the worsening symptoms of RRMM.

B.1.3.4 Clinical management of TCE RRMM and place of teclistamab in the treatment pathway

Treatment guidelines

A variety of European, US and worldwide guidelines are available in the MM disease area, including:[93] the European Haematology Association (EHA) and the European Society for Medical Oncology (ESMO),[94] and the National Comprehensive Cancer Network (NCCN).[95] Of note, these international guidelines recommend the use of a number of novel treatment options which are not currently available in UK clinical practice. This results in the treatment pathway for multiple myeloma in the UK being notably distinct to other countries in Europe, with management of TCE RRMM in the UK primarily informed by NICE's guidelines for the treatment of RRMM [NG35][96], which are discussed in more detail below.

Current UK clinical pathway

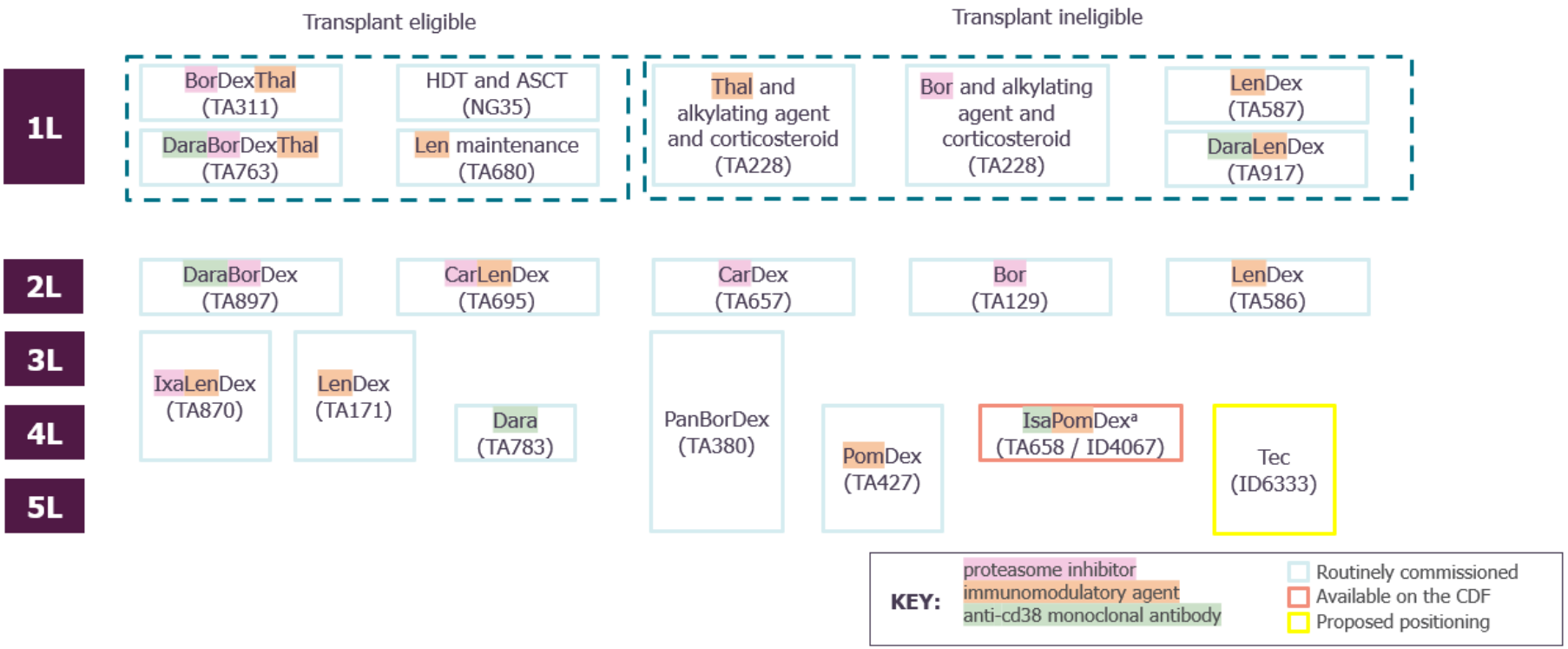
In the current NICE treatment guidelines, patients with newly diagnosed MM are initially assessed for suitability for autologous stem cell transplantation and are typically treated with daratumumab (an anti-CD38 mAb) in combination with bortezomib (a PI), thalidomide (an IMiD), or dexamethasone (a glucocorticoid).[97, 98] Patients who are ineligible for autologous stem cell transplantation would typically receive treatment with daratumumab in combination with lenalidomide (an IMiD) and dexamethasone.[97]

In patients whose disease progresses such that they become relapsed/refractory, treatment in the UK is highly individualised and dependent on eligibility and response to previous treatment, and patients are treated with the same selection of options regardless of autologous stem cell transplant eligibility. Patients will receive treatment with the following three classes of treatment in a varying order and in varying combinations:[97]

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

Treatments recommended by NICE for patients with MM are outlined in Figure 6.[97] Due to the disease pathophysiology, patients do not typically receive treatment of the same drug class 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).

Figure 6: The current NHS MM treatment pathway and proposed positioning of teclistamab



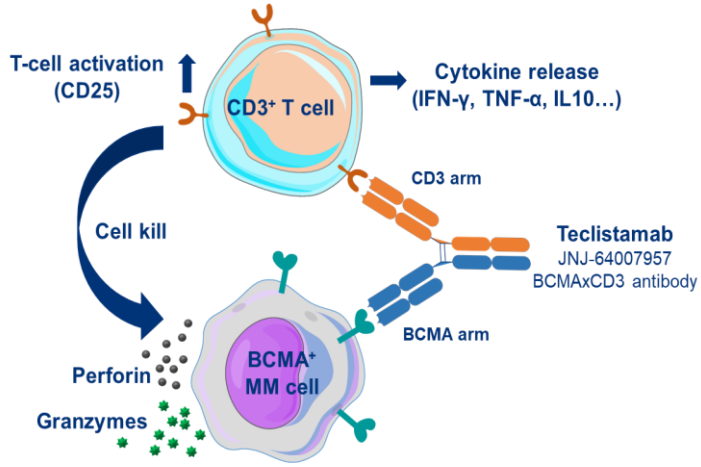
[a] Patients eligible for IsaPomDex must not be refractory to an anti-CD38 mAb, or not previously demonstrated disease progression while receiving an anti-CD38 mAb treatment.
Abbreviations: ½/3/4L: 1st/2nd/3rd/4th line; 5L+: 5th line and beyond; ASCT: autologous stem cell transplantation; Bor: bortezomib; Car: carfilzomib; CDF: Cancer Drugs Fund; Dara: daratumumab; Dex: dexamethasone; HDT: high dose therapy; ID: identification; Isa: 32satuximab; Ixa: ixazomib; Len: lenalidomide; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; Pan: panobinostat: Pom: pomalidomide; TA: technical appraisal; Thal: thalidomide.
Source: NICE Myeloma Diagnosis and Management.[99]

The treatment options recommended by NICE for patients with RRMM who have received three prior therapies have previously been outlined in Table 1; none of these treatments are specifically licensed and recommended for TCE RRMM. As previously detailed in Table 1, in clinical practice, the majority of reimbursed treatments at this stage of disease are either used earlier in the treatment pathway, or are no longer used in this setting due to toxicity.

Positioning of teclistamab within the future UK MM pathway

Teclistamab is a first-in-class, humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody that binds to the B cell maturation antigen (BCMA) present on MM cancer cells and CD3 receptors present on the T cells of the immune system. It works by redirecting a patient's own immune system towards the cancerous tumour cells, attaching and bringing together these two cell types allowing the patient's own immune system to destroy cancerous MM cells.[1]

Figure 7: The mechanism of action of teclistamab



Abbreviations: BCMA: B cell maturation antigen; CD3: cluster of differentiation 3; IFN-y: Interferon gamma; IL10: interleukin 10; MM: multiple myeloma; TNF-a: tumour necrosis factor – alpha.
Source: Source: Adapted from: Ben-Ari (2022).[25]

BCMA is highly and specifically expressed by MM cells, making it a distinct and novel target compared to other approved agents for MM. The dual-binding of teclistamab to both CD3-expressing T cells and BCMA+ cells induces T cell mediated cytotoxicity and myeloma cell death through the recruitment of CD3-expressing T cells to the BCMA expressing cells. This will then mediate T-cell activation and the subsequent target cell lysis of BCMA-expressing myeloma cells.[26] This universal expression of BCMA in the haemopoietic plasma cell pathway not only allows teclistamab to induce myeloma cell death, but also means teclistamab is effective irrespective of clonal heterogeneity.[26]

With this innovative technology and distinct mechanism of action, the reimbursement of teclistamab would introduce a novel class of MM treatment into UK clinical practice – the first new class of treatment since the introduction of the anti-CD38 mAb daratumumab over 5 years ago, which has since become a mainstay of the UK MM treatment pathway.[8, 19, 38, 98, 100]

Unlike many other MM treatment regimens, teclistamab is indicated as a monotherapy, and does not require concomitant treatment with corticosteroids, such as dexamethasone. Dexamethasone

has a significant impact on the daily lives of patients, and as part of the Draft Scope Consultation Comments, Myeloma UK highlighted the value of teclistamab as a dexamethasone-free treatment, noting that dexamethasone can cause mood swings, aggression, mania, insomnia and fatigue, which can be difficult for patients and their families to live with.[101]

Consequently, given the distinctness of teclistamab from other agents in the treatment pathway, together with its high efficacy and favourable safety profile (as detailed in Section B.2), teclistamab represents an ideal candidate for use in RRMM patients in UK clinical practice after three or more prior therapies, as an alternative to PomDex, which could then be saved as a salvage therapy for eligible patients at 5th line.[95] UK clinicians also indicated that owing to the poor survival outcomes of TCE RRMM patients, teclistamab would be used as early as possible in the treatment pathway.[10]

It is therefore anticipated that teclistamab will replace PomDex and become the predominant treatment option for patients with TCE RRMM who have received three prior therapies in UK clinical practice. This positioning is in line with its marketing authorisation: "*as a monotherapy for treatment of RRMM adult patients 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 received*."[29]

Patients with TCE RRMM experience a particularly high symptom burden which increases with each successive LOT, translating to particularly poor HRQoL.[102, 103] Due to the lack of novel treatment options available for TCE RRMM patients, prognosis for these patients is extremely poor, with median OS in this patient population as little as 9.78 months (95% CI: 8.64 to 10.82 months).[24] In the MM-003 trial for PomDex, conducted in patients who were not TCE, only one in three patients responded. Responses were typically shallow and short-lived, with median DOR of 7.5 months and only 7% of patients achieving a VGPR or greater.[85] Given previous exposure to treatments of the same class as currently available therapies, responses would likely be lower in TCE patients. A high unmet need therefore exists in the TCE RRMM patient population for a well-tolerated treatment option, with an effective and novel mechanism of action capable of inducing profound and sustainable responses thus extending PFS and OS, all whilst alleviating symptom burden and enhancing HRQoL.

The recommendation of teclistamab for use in patients with TCE RRMM would address the substantial unmet need described above, providing better disease control and deeper, more sustained responses in TCE RRMM patients, ultimately leading to improvements in patient HRQoL and prolonged survival. Based on modelling estimates, teclistamab is expected to provide patients with an additional extra [redacted] life years gained (LYG) on average, with the potential for this to be much longer for those patients experiencing the best responses.

Ongoing studies and future management of RRMM

The landscape of multiple myeloma is rapidly evolving, with ongoing changes in therapeutic approaches. Teclistamab is already recommended for use across Europe,[28, 39] meaning that its inclusion in the UK's treatment pathway is crucial for maintaining the country's leadership in myeloma innovation and continuing to enhance the health outcomes of MM patients observed over the last decade.

Additionally, several clinical trials ongoing are investigating novel therapeutic agents in heavily pre-treated RRMM patients who typically experience poor disease outcomes such as chimeric antigen receptor T-cells (CAR-T), other bispecific antibodies (such as GPRC5D, FcRH5), inhibitors of XPO1, BCL-2 trispecifics (BCMA and GPRC5D) or antibody-drug coagulates.[104] The recommendation of teclistamab would prime the UK pathway for the introduction of these upcoming novel agents, contributing to ongoing improvement in survival for patients with RRMM.

B.1.4 *Equality considerations*

There are not anticipated to be any equality issues relating to the use of teclistamab in the UK.

B.2 Clinical effectiveness

Clinical efficacy and safety evidence for teclistamab in TCE RMMM are provided by the MajesTEC-1 trial

- The MajesTEC-1 trial (N=165) was a Phase I/II, first-in-human, open-label, multicentre, single-arm trial. UK clinical experts confirmed that patients enrolled in MajesTEC-1 generally represent those with TCE RRMM encountered in UK clinical practice.[105 83]
- Clinicians noted that due to the international nature of the MajesTEC-1 trial, patients in the study were more heavily pre-treated compared to the anticipated patient population who would receive teclistamab in UK clinical practice. As a result, the observed efficacy outcomes for teclistamab may be on the conservative side.
- Furthermore, the MajesTEC-1 trial took place during the height of the COVID-19 pandemic, with only a small percentage (7.9%) of patients having received a COVID-19 vaccine prior to their first dose of teclistamab.[106] Considering the impact of excess mortality caused by COVID-19, the survival results reported in MajesTEC-1 are likely to be conservative.

Teclistamab rapidly induces deep and durable responses among TCE RRMM patients that translated to prolonged progression-free survival and overall survival outcomes

- ORR was the primary endpoint of the MajesTEC-1 trial. Teclistamab induces being clinically meaningful, high and deep responses in a disease resistant to all mainstream treatments, with an overall response rate (ORR) of 63.0% (95% CI: [redacted]).[105] This ORR represents the highest magnitude of clinical benefit that can be achieved within off-the-shelf immunotherapy options based on the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies.[107]
    - Almost all responders achieved a VGPR or better (98/104); the ≥VGPR rate in MajesTEC-1 was 59.4% (95% CI: [redacted]).
    - Overall, 46.1% of patients achieved a complete response or better (≥CR) (95% CI: [redacted]) (including 38.8% of patients achieving a stringent complete response [sCR] [95% CI: [redacted]]).
    - Recent RWE studies found that the results observed in MajesTEC-1 are generalisable to clinical practice, reporting ORRs to teclistamab of 59.3% and 64% in patients with TCE RRMM in clinical practice[108]
- Responses to teclistamab are durable and deepen over time. For patients who achieved a response, the median duration of response was 24.0 months (95% CI: 17.0, NE). Amongst the 76 patients who achieved a CR or better, median DoR was NE (95% CI: [redacted]) and the 24-month DOR rate for these patients was [redacted]).[105]
- In MajesTEC-1, minimal residual disease (MRD) negativity was achieved by 29.1% of patients; 48 of the 56 MRD-evaluable patients (85.7%) achieved MRD negativity at 10^{-5}.[105]
- As per the August 2023 DCO, median progression-free survival (PFS) and overall survival (OS) were 11.4 months (95% CI: 8.8, 16.4) and 22.2 months (95% CI: 15.1, 29.9), respectively.[107]
    - Amongst the 76 patients who achieved a CR or better, median PFS was NE (95% CI: [redacted]), with a 24-month PFS rate of [redacted])[105]
    - Amongst the 76 patients who achieved a CR or better, median OS was NE (95% CI: [redacted]) and the 24-month OS rate was [redacted]

Indirect treatment comparison (ITC) using IPD from the UK RW TCE cohort study and MajesTEC-1 shows consistent clinical benefit of teclistamab versus PomDex

- There are no published clinical trial data for PomDex for patients with TCE RRMM who have received at least three prior therapies. As such, aligned with the accepted approach in TA889, Janssen gathered real-world data for patients with TCE RRMM receiving PomDex in UK clinical practice.
- In the base case ITC approach, the MajesTEC-1 cohort was reweighted to match the UK RW study via inverse probability of treatment weighting (IPTW) in line with NICE TSD 17[109]
- The deep response with teclistamab resulted in a statistically significant and clinically meaningful improvement in PFS [based on TTNT as a proxy] (HR: 0.56; 95% CI: 0.40, 0.79), translating to an improvement in median PFS of 5.36 months (12.39 versus 7.03 months; representing a 76.2% increase). Thus, treatment with teclistamab reduces the risk of progression or death by 44% compared to PomDex.
- The prolonged PFS translated to a statistically significant and clinically meaningful improvement in OS (HR: 0.52; 95% CI: 0.36, 0.74) i.e., 48% reduction in the risk of death, and an improvement in median OS of 12.43 months (22.21 versus 9.78 months; representing a 2.27-fold increase)
- These results were consistent across an extensive range of sensitivity analyses (which varied the IPTW approach and number of prognostic factors adjusted for).
- Furthermore, the base case analysis produced the most conservative results of all sensitivity analyses, consequently representing the upper bound to the relative efficacy between teclistamab and PomDex.

Teclistamab delivers on patients' expectations with [redacted] in HRQoL, including [redacted] global health status and decrease in pain and fatigue

- Health-related quality of life (HRQoL) for patients with MM significantly deteriorates with each relapse and line of therapy[69]
- Patients with TCE RRMM experience a significant symptomatic burden coupled with high levels of emotional distress and often experience high anxiety, with one in five patients worrying about dying given all effective treatment options have been exhausted in UK clinical practice.[34]
- Teclistamab was associated with [redacted] in HRQoL over time, as indicated by [redacted] from baseline in MM-related symptoms such as pain and fatigue, global health status, and functioning measured by:[105]
    - European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L) VAS score: The LS mean improvement in EQ-5D-5L VAS score from baseline to Cycle 12 in the mixed model for repeated measures was [redacted] (95% CI: [redacted], [redacted])
    - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30) score: Meaningful improvement from baseline to Cycle 12 was reported by [redacted]% of subjects for global health status, [redacted]% of subjects for physical functioning, [redacted]% of subjects for fatigue, and [redacted]% of subjects for pain score
    - Patient Global Impression of Severity (PGIS) scores: [redacted]% and [redacted]% of patients reporting severity as none or mild at Baseline – which increased to [redacted]% and [redacted]% at Cycle 6, and to [redacted]% and [redacted]% at Cycle 12

Teclistamab is well tolerated, with few patients discontinuing treatment or requiring dose reductions due to AEs

- Teclistamab was well tolerated overall, with AEs rarely leading to dose reduction or treatment

discontinuation (<5% discontinued teclistamab due to an AE).[105]

- The most frequently reported treatment-emergent AEs were cytopenias, infections and cytokine release syndrome (CRS). AEs were effectively managed with available treatment, with the step-up dosing schedule used to mitigate risk of severe CRS. Infection rates were reduced over time by switching to Q2W dosing.[110]
- Clinical experts suggested that the safety profile of teclistamab has improved since the initiation of MajesTEC-1 as clinicians are more experienced in delivering and managing the safety profile of teclistamab as well as the widespread availability of COVID-19 vaccinations.[83, 105]

Conclusions

- Teclistamab meets the substantial unmet need in patients with TCE RRMM for an effective and well-tolerated treatment option. With its novel mechanism of action, teclistamab induces profound and enduring responses, leading to clinically significant enhancements in PFS and OS compared to PomDex, the current treatment used to manage TCE RRMM in the UK.

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). The original clinical SLR search was conducted on the 26th May 2020 and updated on the 22nd January 2021. All searches were subsequently updated in April 2022, May 2022 and February 2023, with the most recent update conducted on the 31st October 2023.

Following de-duplication of results, a total of 4,895 records across all searches were screened at the title and abstract stage, of which 2,204 records were reviewed at the full-text stage. After exclusion of records not meeting the eligibility criteria, 455 records (reporting on 218 unique studies) were included in the SLR. A complete list of the 455 included records is presented in Appendix D.1. 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.[111]

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical SLR identified one study of teclistamab in the patient population of interest to this submission, which was past the recruitment stage at the time of the SLR, the MajesTEC-1 clinical trial.

Teclistamab holds a marketing authorisation for use in adult patients with RRMM who have received at least three prior therapies, and have demonstrated disease progression on the last therapy.[27] MajesTEC-1 was the registrational trial supporting the licence application for teclistamab and therefore forms the principal source of efficacy data for this submission.[112, 113]

MajesTEC-1 is an ongoing Phase I/II, open-label, single-arm, multicentre study investigating the safety and efficacy of teclistamab as a monotherapy in adult patients with TCE RRMM.[105] The study commenced in 2017 and is the first in-human Phase I/II study of teclistamab. The data presented in this submission are based on the [redacted] datacut (August 2023) of MajesTEC-1 .[105] An overview of MajesTEC-1 is presented in Table 4.

The eligibility criteria for MajesTEC-1 were slightly broader than the population of relevance for this submission, as further explained in Section B.2.3.1, also including a cohort of patients previously treated with an anti-B cell maturation agent (BCMA) (Cohort C; see Figure 8). This cohort of patients does not exist in the UK as there are currently no BCMA treatments established in UK routine clinical practice. As such, the evidence included in this submission does not include patients who had previously received treatment with an anti-BCMA.

Table 4: Clinical effectiveness evidence

Study	MajesTEC-1 (NCT03145181 for Phase I; NCT04557098 for Phase II)[114,115]
Study design	A Phase I/II open-label, multicentre, single-arm trial assessing the safety and efficacy of teclistamab 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 RP2D dose expansion
Population	Of relevance to this submission: adult patients with RRMM who have received previous treatment with an IMiD, PI and mAb who received teclistamab at the licensed Phase II dose (including 40 patients from the Phase I portion of the study and 125 patients in Cohort A from the Phase II portion)
Intervention(s)	Phase I (Part 1) dosing: • Teclistamab IV: 0.0003 to 0.0192 mg/kg Q2W and 0.0192 to 0.72 mg/kg weekly • Teclistamab SC: 0.08 to 1.5 mg/kg weekly Phase I (Part 2) dosing: • Teclistamab IV: 0.72 mg/kg weekly • Teclistamab SC: 1.5 mg/kg weekly Phase II dosing: • Teclistamab 1.5 mg/kg SC weekly • Patients were permitted to switch to biweekly SC 1.5 mg/kg dosing, as per the protocol amendment on the 5th July 2021, upon meeting the following criteria:[a] • Phase I: Patients were required to have confirmed PR or better and have received a minimum of four cycles of treatment • Phase II: Patients were required to have a response of CR/sCR for a minimum of six months Teclistamab 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's first dose)
Comparator(s)	N/A – At the time of the study initiation date (16th May 2017), there were no regulatory-approved therapies specifically indicated for patients with TCE RRMM and RWE demonstrated a lack of SoC in this setting. As such, MajesTEC-1 was designed as a single-arm trial.[79, 116] Single-arm study designs are common in early phase oncology trials, in particular for rare conditions with high unmet needs, such as TCE RRMM where standard-of-care treatments do not exist. The subsequent regulatory approval of 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.[117-123]

Study	MajesTEC-1 (NCT03145181 for Phase I; NCT04557098 for Phase II)[114,115]
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[b]	• **Overall survival (OS)**
	• **Progression-free survival (PFS)**
	• Response rates:
	  ○ Overall response rate (ORR)
	  ○ Stringent complete response (sCR)
	  ○ Complete response (CR) or better
	  ○ Very good partial response or better (≥VGPR)
	  ○ Partial response (PR)
	  ○ Minimal response (MR)
	  ○ Stable disease (SD)
	  ○ Progressed disease (PD)
	• **Adverse events (AEs)**
	• Health-related quality of life (HRQoL) outcomes;
	  ○ European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30) scores
	  ○ **European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L) scores**
	  ○ Patient Global Impression of Severity (PGIS) scores

All other reported outcomes[b]	• **Time to treatment discontinuation (TTD)** • **Time to next treatment (TTNT)** • Duration of response (DOR) • Dose-limiting toxicity (DLT) • Minimal residual disease (MRD) negativity rate

[a] Patients were also 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 six months (Phase II). Patients were also permitted to switch to less frequent dosing to manage toxicity per investigator discretion. [b] Bolded outcomes are included in the economic model.
Abbreviations: CR: complete response; DOR: duration of response; DLT: dose-limiting toxicity; 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; IV: intravenous; MR: minimal response; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PD: progressed disease; PGIS: Patient Global Impression of Severity; PR: partial response; RP2D: recommended Phase II dose; RRMM: relapsed/refractory multiple myeloma; RWE: real-world evidence; SC: subcutaneous; sCR: stringent complete response; SD: SoC: standard of care; stable disease; TCE: triple-class exposed; TTD: time to treatment discontinuation; TTNT: time to next treatment; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

MajesTEC-1 is a three-part Phase I/II, open-label, single-arm study conducted at multiple sites across Europe (including three study centres in the UK), US, Canada and China in patients >18 years of age with TCE RRMM with disease progression.[105] An overview of the MajesTEC-1 trial design is provided in Figure 8.

An overview of the primary objectives of the three parts of MajesTEC-1 is provided below:[124, 125]

- **Phase I (Part 1, dose escalation):** To identify the proposed recommended Phase II dose(s) (RP2D) and accompanying schedule assessed to be safe for teclistamab
- **Phase I (Part 2, dose expansion):** To characterise the safety and tolerability of teclistamab at the proposed recommended Phase II dose (RP2D)
- **Phase II (Part 3):** To evaluate the efficacy and safety of teclistamab at the RP2D (and subsequently licenced) in TCE patients with RRMM who had previously received ≥3 prior lines of therapy

Figure 8: MajesTEC-1 trial design

[a] For doses A, B and C, escalation only occurred if there was no Grade 2 or higher toxicity. [b] Patients in Phase II were permitted to switch to biweekly dosing as per the protocol amendment on the 21st July 2021. [c] At the time of the [redacted] August 2023 DCO, Cohort B was not open for enrollment.
Abbreviations: ACD: antigen antibody-drug conjugate; BCMA: B-cell maturation antigen; IMiD: immunomodulatory agent; mAb: monoclonal antibody; ORR: overall response rate; PI: proteasome inhibitor; QW: once weekly; R2PD: recommended Phase II dose; SC: subcutaneous.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Patient cohorts (Phase II only)

The RP2D of teclistamab based on the Phase I portion of the study, was 1.5 mg/kg administered by subcutaneous (SC) injection weekly until disease progression or unacceptable toxicity occurs. Treatment doses were preceded by SC step-up doses of 0.06 and 0.3 mg/kg on Days three and five.[27]

Based on the RP2D from Phase I, three cohorts of patients were enrolled into the Phase II portion of the study. Descriptions of the patient cohorts are provided in Table 5.

At the time of the [redacted] data cut-off (DCO) (August 2023) of MajesTEC-1, Cohort B was not open for enrolment. Cohort C included patients treated with an anti-BCMA treatment. No anti-BCMA treatments are recommended for use in UK clinical practice, and therefore these patients are not reflective of any patient groups in the UK. As such, this cohort was not considered relevant for this submission. Therefore, Cohort B and Cohort C are not discussed further in this submission.

As such, 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 make up the cohorts used to inform the clinical efficacy and safety of teclistamab in this submission. These patients are collectively referred to as **the All Treated Analysis Set (N=165),** which is the same population of patients used to inform the marketing authorisation for teclistamab.[27] Full details of the analysis sets in MajesTEC-1 are presented in Section B.2.4.2.

Table 5: Patient cohorts in MajesTEC-1

Patient cohort	Description	Number of patients
Included in the submission		
Phase II (Cohort A)	Patients with RRMM who received ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb (TCE)	N=125
Phase I (RP2D Cohort)	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)	N=40
Not included in the submission		
Phase II (Cohort B[a])	Patients that were heavily pre-treated (≥4 lines of therapy)	N=0
Phase II (Cohort C)	Patients with RRMM who received ≥3 prior lines of therapy that included a PI, an IMiD, anti-CD38 mAb and anti-baseline B-cell maturation (BCMA) treatment (chimeric antigen receptor [CAR]-T cells or an antibody drug conjugate [ADC])	N=40

[a] At the time of this submission, enrolment is not open for Cohort B
Abbreviations: ADC: antibody drug conjugate; IMiD: immunomodulatory drug; mAb: monocloncal antibody; PI: proteasome inhibitor; RRMM: relapsed/refractory multiple myeloma; TCE: triple-class exposed.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.3.2 Trial methodology

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

Table 6: MajesTEC-1 trial design and methodology

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
Key Inclusion/exclusion criteria (for the All Treated Analysis Set of relevance to this submission)	**Inclusion criteria:** • ≥18 years of age • Documented diagnosis of MM according to IMWG diagnostic criteria[126] • 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-targeted 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 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[126]
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:[b] • 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

Pre-planned subgroups	• Sex (male versus female)
	• Age
	• Baseline renal function
	• Baseline hepatic function (normal versus impaired[c])
	• Race
	• Baseline ECOG performance score (0 versus ≥1)
	• Number of lines of prior therapy (≤3 versus >3)
	• 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)
	• Prior allogenic stem cell transplant (yes versus no)
	• Type of myeloma (IgG versus non-IgG)
	• Baseline International Staging System (ISS)[d]
	• Baseline revised ISS (R-ISS)[e]
	• Cytogenetic risk (high-risk[f] versus standard-risk)
	• Bone marrow % plasma cells
	• Extramedullary plasmacytomas (0 versus ≤1)

Duration of study and follow-up	The first patient in the study was treated on 16th May 2017 and at the latest DCO (August 2023), the median duration of follow-up was 30.4 months (range [redacted]) for the All Treated Analysis Set.

[a] Results from Cohort B and C are not presented in this submission for the reasons noted in Section B.2.3.1. [b] Results from the exploratory outcomes are not included in this submission. [c] Includes mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5×ULN), moderate (1.5×ULN < total bilirubin ≤ 3×ULN), severe (total bilirubin > 3×ULN). [d] Baseline ISS was derived based on the combination of serum β2-microglobulin and albumin. [e] Baseline R-ISS will be derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level (LDH). [f] High risk is defined by patients having t (4; 14); t (14; 16) and/or 17p deletion.
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: strigent complete response; TTNT: time to next treatment; UK: United Kingdom; US: United States; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO);[105] MajesTEC-1 Clinical Protocol.[125]

B.2.3.3 Baseline characteristics of trial patients

Data presented in this section are based on patients who received the RP2D of teclistamab in Phase I (n=40) or were in Cohort A in Phase II (n=125) of MajesTEC-1, together forming the All Treated Analysis Set (N=165). A summary of baseline demographic and disease characteristics of patients in the All Treated Analysis Set of MajesTEC-1, is provided in Table 7 below. A summary of prior treatment history of patients in the All treated Analysis Set is provided in Table 8.

Patients had a median age of 64 years (range, 33 to 84). The median time between diagnosis and the first dose was 6 years (range, 0.8 to 22.7). Extramedullary disease (defined as the presence of one or more extramedullary soft-tissue lesions) was present in 28 patients (17.0%). Among the 148 patients with available cytogenetic data, 38 (25.9%) had at least one high-risk cytogenetic abnormality. Patients had received a median of 5 previous lines of therapy (range, 2 to 14), and 116 (70.3%) had received at least two immunomodulatory agents, at least two proteasome inhibitors, and at least one anti-CD38 antibody (penta-drug exposure). Before study entry, 148 patients (89.7%) had resistance to the previous line of therapy, 128 (77.6%) had triple-class refractory disease, and 50 (30.3%) had penta-drug refractory disease.

The generalisability of the MajesTEC-1 trial population to UK clinical practice was informed by interviews with UK clinical experts conducted in December 2023, as well as comparison versus the characteristics of patients in the UK RW TCE cohort study (detailed in Section B.2.9). Overall, UK clinical experts considered that the baseline characteristics of patients in MajesTEC-1 were broadly generalisable to the population of patients expected to receive teclistamab in UK clinical practice.[83] The generalisability of the patient population is further supported by MajesTEC-1 having three study centres in the UK.

One of the differences highlighted by the UK clinical experts was that due to the international nature of the MajesTEC-1 trial, patients were more heavily pre-treated, with a median number of 5 lines of prior therapy. This characteristic indicates that these patients may have a higher-risk disease and possibly worse outcomes compared to patients who would receive teclistamab in UK clinical practice. As such, the clinical experts pointed out that the efficacy data from the MajesTEC-1 trial may provide a conservative estimation of the genuine efficacy of teclistamab in UK clinical practice.[83]

With regard to other characteristics:

- As MM most commonly occurs in men, the slightly higher proportion of males in MajesTEC-1 (58.2%), as reported in Table 7, is in line with UK clinical practice (See Section B.1.3.2).[58, 124]
- The average age of patients in MajesTEC-1 is slightly lower than the age of TCE RRMM patients in UK clinical practice, as reported in the UK RW TCE cohort study (64 vs 71 years respectively). However, UK clinical experts highlighted that a cohort of younger TCE RRMM patients likely present in UK clinical practice, as older or frailer patients typically do not receive four or more lines of treatment.[83] In particular, it was noted that this younger subset of patients likely make up a large proportion of the patients who are eligible for fourth line treatment. As such, the mean age of patients in MajesTEC-1 is considered broadly generalisable to the anticipated eligible patient population for teclistamab in UK clinical practice.

- Clinicians highlighted that the median time since diagnosis of patients in MajesTEC-1 was aligned with that of patients who would receive teclistamab in UK clinical practice.[83]
- Patients eligibility in MajesTEC-1 included ECOG score of 0−1 (Table 7). Due to MajesTEC-1 being the first-in-human trial of teclistamab, and based on pre-clinical data informing the potential safety profile with regards to T-cell activation and targeting of B cells and the risk of cytokine release syndrome (CRS), it was considered appropriate to restrict the inclusion criteria to ECOG 0−1 whilst a greater understanding of the molecule was developed. Having a restricted ECOG population is a common limitation of early phase oncology trials and therefore is not considered to represent a major generalisability concern to the NHS TCE RRMM population. This is supported by the results of Dima et al. (2023), a real-world study of patients receiving teclistamab in clinical practice. Of the N=102 patients included in Dima *et al.* (2023), 80% would not have met the MajesTEC-1 eligibility criteria for reasons including an ECOG PS ≥2 (28%), Grade 3-4 anaemia (26%) and Grade 3-4 thrombocytopenia (20%).[127] Importantly, the study reported efficacy results consistent with those observed in MajesTEC-1
- UK clinical experts in RRMM noted that overall, the distribution of prior therapies of patients in MajesTEC-1 were in line with clinical expectations for TCE RRMM patients in UK clinical practice, despite patients in MajesTEC-1 being more heavily pre-treated. The majority ([redacted]%) of patients in the All Treated Analysis Set of MajesTEC-1 had received three or more lines of prior therapy and, in line with the trial eligibility criteria, all patients had received prior treatment with a PI, IMiD and an anti-CD38 mAb (Table 8). As such, the patient population of the MajesTEC-1 trial is in line with the population of relevance to this submission and the license wording for teclistamab (see Table 3, Section B.1.2).
- In terms of refractoriness, 89.7% of patients in the All Treated Analysis Set were refractory to their last line of prior therapy, with 77.6% refractory to a PI, IMiD and an anti-CD38 mAb (Table 8).[124] Whilst these levels of refractoriness are slightly higher than expected in UK clinical practice, refractoriness levels to a PI, IMiD and an anti-CD38 mAb are anticipated to increase in future years, owing to the recent positive recommendations of DaraLenDex [TA917] and DaraBorDex [TA897], thereby emphasising the unmet need for new treatments with novel mechanisms of action in this setting.[19, 100]
- Finally, the proportion of patients in the All Treated Analysis Set who had previously received autologous stem cell transplantation (ASCT) (81.8%) was higher than the data from the UK RW TCE cohort study (81.8% vs 34.2%).[24] It can be expected that in UK clinical practice, patients who reach fourth-line treatment with TCE RR status, may be younger with varying disease biology and thus more likely to have received a previous ASCT. Nonetheless, UK clinical experts unanimously agreed that prior ASCT history does not represent a significant prognostic factor at this line of therapy and in this patient population (i.e., TCE RRMM). This is explained by the considerable time elapsed since ASCT and the subsequent lines of therapy used, thereby ensuring that these differences are not anticipated to affect the generalisability of the trial results.[83, 128]

Table 7: Baseline characteristics and demographics in MajesTEC-1

Baseline Characteristic	All Treated Analysis Set (N=165)
Age, years	
Mean (SD)	[redacted]

Median (range)	64.0 (33, 84)
≥75 years, n (%)	24 (14.5%)
Sex	
Female, n (%)	69 (41.8%)
Male, n (%)	96 (58.2%)
Race, n (%)	
Asian	3 (1.8%)
Black or African American	21 (12.7%)
White	134 (81.2%)
Multiple	[redacted]
Other	[redacted]
Not reported	[redacted]
Weight, kg	
Mean (SD)	[redacted]
Median (range)	[redacted]
ECOG Performance Status score prior to infusion, n (%)[a]	
0	55 (33.3%)
1	[redacted]
3	[redacted]
Type of myeloma by immunofixation or serum FLC assay, n (%)	
IgG	[redacted]
IgA	[redacted]
IgM	[redacted]
IgD	[redacted]
IgE	[redacted]
Light chain	[redacted]
Kappa	[redacted]
Lambda	[redacted]
FLC-Kappa[b]	[redacted]
FLC-Lambda[c]	[redacted]
Biclonal	[redacted]
Negative immunofixation	[redacted]
Type of measurable disease, n (%)	
Serum only	[redacted]
Serum and urine	[redacted]
Urine only	[redacted]
Serum FLC	[redacted]
Not evaluable	[redacted]
ISS Staging, n (%)[d]	
Stage I	85 (52.5%)
Stage II	57 (35.2%)

Stage III	20 (12.3%)
R-ISS Staging, n (%)[e]	
Stage I	[redacted]
Stage II	[redacted]
Stage III	[redacted]
Time from MM diagnosis to first dose, years	
Mean (SD)	[redacted]
Median (range)	6.0 (0.8, 22.7)
Number of lytic bone lesions, n (%)	
None	[redacted]
1−3	[redacted]
4−10	[redacted]
More than 10	[redacted]
Number of extramedullary plasmacytomas, n (%)[f]	
0	137 (83.0%)
≥1	28 (17.0%)
% Plasma cells, bone marrow biopsy/aspirate[g]	
<5	[redacted]
≥5 – ≤30	[redacted]
>30 – <60	[redacted]
≥60	[redacted]
Cytogenetic risk, n (%)	
Standard risk	[redacted]
High risk	[redacted]
del(17p)	23 (15.5%)
t(4;14)	16 (10.8%)
t(14;16)	4 (2.7%)
Bone marrow cellularity biopsy, (%)	
Hypercellular	[redacted]
Normocellular	[redacted]
Hypocellular	[redacted]
Indeterminate	[redacted]

[a] One patient with an ECOG score of 3 being included in the trial was a protocol violation. [b] Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing. [c] Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing. [d] ISS staging is derived based on serum β2-microglobulin and albumin. [e] R-ISS is derived based on the combination of serum β2-microglobulin and albumin, genetic risk, and level of lactate dehydrogenase level (LDH). [f] 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. [g] 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: Janssen. Data on File. MajesTEC-1 Clinical Study Report (March 2022 DCO);[129] Moreau *et al*. (2022).[112]

Table 8: Prior therapies in MajesTEC-1

	All Treated Analysis Set (N=165)
Number of prior LOT, n (%)[a,b]	
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
>5	[redacted]
Mean (SD)	[redacted]
Median (range)	5.0 (2.0, 14.0)
Prior hematopoietic stem cell transplantation	
Autologous	135 (81.8%)
1	[redacted]
≥2	[redacted]
Allogenic	[redacted]
Other prior treatments	
Prior PI + IMiD + anti-CD38 mAb	165 (100.0%)
Prior penta-exposed (2 Pis, 2 IMiDs, anti-CD38 mAb)	116 (70.3%)
Refractory Status, n (%)	
Refractory at any point to prior therapy	[redacted]
Refractory to last line of prior therapy	148 (89.7%)
Refractory to treatment, n (%)	
Any PI	142 (86.1%)
Any IMiD	152 (92.1%)
Any anti-CD38 mAb	148 (89.7%)
Double (PI + IMiD)	133 (80.6%)
Triple (PI + IMiD + anti-CD38 mAb)	128 (77.6%)
Penta (2 Pis, 2 IMiDs, anti-CD38 mAb)	50 (30.3%)

[a] Based on data recorded on prior systemic therapy eCRF page. [b] Included 3 patients in Phase I (for whom no minimum for prior lines of therapy was established per protocol) and 2 patients in Phase II who were enrolled under the protocol amendment 9 for whom having 2 prior lines of therapy was permitted.
Abbreviations: IMiD: immunomodulatory drug; mAb: monoclonal antibody; MM: multiple myeloma; LOT: line of therapy; PI: proteasome inhibitor; SD: standard deviation.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (September 2021 DCO).[130]. Moreau *et al*. (2022).[112]

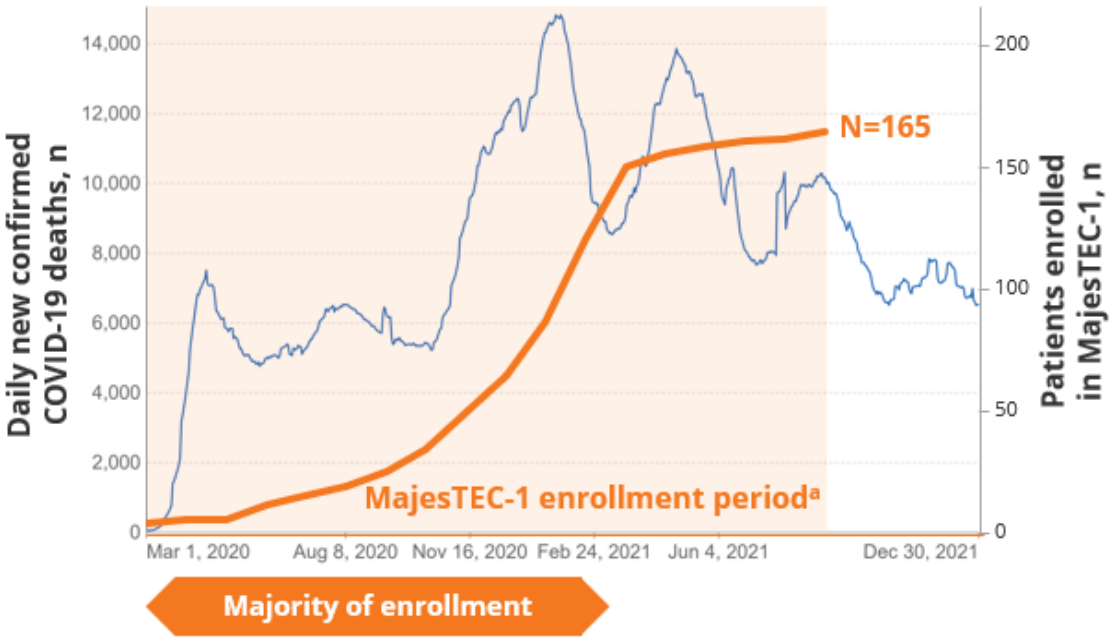
B.2.4 *Statistical analysis and definition of analysis sets in the relevant clinical effectiveness evidence*

B.2.4.1 Study population and patient disposition

Patients were enrolled in MajesTEC-1 between the 8th June 2017 and the 13th August 2021 across 35 sites in nine countries, including three study sites in the UK.

On the 11th March 2020, the World Health Organization declared the novel coronavirus outbreak as a global pandemic. Of note, the majority of the enrolment period for MajesTEC-1 therefore occurred during the peak of the COVID-19 pandemic, as depicted in Figure 9 below. This period coincides with COVID-19 becoming the 3rd leading cause of death in the US, while global daily deaths from the virus exceeded 14,000. In the UK, [131] steroids were used to reduce mortality in severe cases, until the commencement of the mass vaccination programme in December 2020, which aimed to protect the most clinically vulnerable individuals, such as TCE RRMM patients.[132] The impact that the COVID-19 pandemic had on the results of MajesTEC-1 is discussed in Section B.2.10.2.

Figure 9: COVID-19 worldwide deaths during MajesTEC-1 enrolment



Source: Donk *et al.* (2023).[131]

The main population of patients in MajesTEC-1 used to inform the efficacy evidence is the All Treated Analysis Set (N=165), as defined in Section B.2.3.1, with a clinical cut-off of August 2023.[105] All patients received at least one dose of teclistamab at the licensed dose of 1.5 mg/kg.

As of the [redacted] August 2023 DCO, 38 patients (23.0%) were still receiving teclistamab, while 127 patients (77.0%) had discontinued treatment.105 TEAE leading to treatment discontinuation was reported for 9 patients (4.8%).[105] A diagram of the patient disposition in MajesTEC-1 is provided in Figure 10 below.

Figure 10: Patient disposition in MajesTEC-1 (August 2023 DCO)

Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.4.2 Statistical analyses

Analysis sets

A summary of the analysis sets in MajesTEC-1 relevant to this submission are presented in Table 9. A total of 165 patients were included in the All Treated Analysis Set, which forms the primary analysis set for the efficacy and safety analyses presented in this submission. Additionally, patient-reported outcomes (PROs) were collected for 125 patients in Phase II, Cohort A of the trial, making up the PRO Analysis Set.[105]

Table 9: Summary of relevant analysis sets in MajesTEC-1

Analysis Set	MajesTEC-1	Number of patients
All Treated Analysis Set	Patients who received at least 1 dose of study intervention, including 40 patients enrolled into the Phase I portion of the study and 125 enrolled into Cohort A	N=165
PRO Analysis Set	Patients enrolled in Phase II Cohort A of the study. PROs were not assessed in Phase I.	N=125

Abbreviations: PRO: patient-reported outcomes Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Details of the statistical methods for both the Phase I and Phase II primary analyses in MajesTEC-1 are presented in Table 10.

Table 10: Statistical methods for the primary analysis of MajesTEC-1

Trial name	MajesTEC-1
Hypothesis objective	**Phase I** • The primary objective of the Phase I portion of the study was to determine the safety of teclistamab, as characterised by the frequency and type of dose-limiting toxicity, and occurrence and severity of AEs, SAEs and laboratory values **Phase II** • The primary objective in the Phase II portion of the study was to evaluate the efficacy and safety of teclistamab • The primary endpoint was ORR, defined as a PR or better according to the criteria of the IMWG,[126] as assessed by an IRC
Statistical analysis	• Analysis of ORR was based on the efficacy analysis set. Patients with no post-baseline data were considered as non-responders. Response after the start of subsequent therapy with teclistamab was not considered. The ORR and its 2-sided 95% exact CI for each cohort are presented • In Phase II of the trial, the response rates and 95% exact CI for the primary endpoint were calculated based on binomial distribution, with null hypothesis rejected if the lower bound of CI>30% • For the assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis of the primary efficacy endpoint of ORR for the prespecified subgroups was conducted • Subgroups investigated included analysis to assess whether specific molecular subgroups such as del17p, t(4;14), t(14;16) or other risk associated mutations/translocations are responsive to treatment • Subgroup results 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) • Kaplan–Meier (KM) methods were used to estimate time to-event endpoints (DoR, PFS and OS) • HRQoL assessments were analysed using descriptive statistics
Sample size, power calculation	• For the Phase I part of MajesTEC-1, at least 6 patients were required to assess safety and confirm the teclistamab dose • In Part 2 of Phase I, up to 40 patients were required to receive teclistamab at the proposed licensed dose determined in Part 1 to further assess its safety and tolerability as well as preliminary antitumor

	activity. This therefore provided a high probability of observing at least one toxicity, with the true adverse event rate being as low as 10% • In Part 3 of MajesTEC-1, as it was estimated that there would be approximately 100 patients treated with teclistamab in Cohort A, it was estimated that there would be >85% power to declare the ORR was higher than 30% at the one-sided significance level of 0.025 with the assumption that ORR among those treated with teclistamab was at least 45%
Data management, patient withdrawals	**Discontinuation and withdrawal:** • If a patient discontinued study drug and withdrew from the study, end of treatment assessments were obtained. The reason(s) a patient discontinued treatment was recorded on the electronic case report form (eCRF) and source documents • If a patient was lost to follow-up, every reasonable effort was 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 • Study drug assigned to the withdrawn patient was not assigned to another patient • Patients who withdrew for reasons other than toxicity were replaced at the discretion of the sponsor **Data censoring was applied for the outcomes analysis as follows:** • For DoR calculation in patients who did not progress, data was censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy • For the PFS calculation, patients who did not progress and who were alive, data was censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy • For the OS calculation, if the patient was alive or the vital status was unknown, then their data was censored at the date the patient was last known to be alive

Abbreviations: CI: confidence interval; DoR: duration of response; eCRF: electronic case report form; HRQoL: health-related quality of life; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO);[105] Janssen Data on File. MajesTEC-1 Study Protocol;[125] Janssen Data on File. Statistical Analysis Plan.[133]

Definitions of outcome measures

A variety of outcomes were employed in MajesTEC-1 to explore the efficacy of teclistamab in TCE adult patients with RRMM. Definitions for these outcome measures are presented in Table 11.

Table 11: Definitions for outcome measures used in MajesTEC-1

Outcome measure	Definition
Primary outcome	
ORR (Phase II only)	Defined as the proportion of patients who achieved PR or better according to IMWG criteria, as assessed by the IRC.
Key secondary outcomes	
DOR[a]	Calculated among responders (with a PR or better) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria, or death due to progressed disease (PD), whichever occurred first. Duration of response was calculated by replacing death due to progression with death from any cause.
Occurrence and severity of AEs, SAEs and laboratory values[a]	An AE was classed as any unexpected medical event that occurred in a participant who was administered an investigational product, and it did not necessarily indicate only those events with a clear causal relationship with the relevant investigational product. A serious AE (SAE) was defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and European Guidelines on Pharmacovigilance for Medicinal Products for Human Use.[134]
Time to response (TTR)	Defined as the time between date of first dose of study intervention and the first efficacy evaluation that the participant has met all criteria for PR or better. Time to best response is defined as the time between date of first dose of study intervention and the first efficacy evaluation that the participant has his/her best response to treatment. Time to CR or better is defined as the time between date of first dose of study intervention and the first efficacy evaluation that the participant has met all criteria for CR or better and for time to VGPR or better it is once the participant has met all criteria for VGPR or better.
OS	Defined as the time from the date of first dose of study intervention to the date of the participant's death, due to any cause. Patients who are lost to follow-up will be censored at the time of lost to follow-up. Patients who died after consent withdrawal but with death data collected as allowed by applicable regulations will be considered as having an OS event. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.
TTNT	Defined as the time from the date of the first dose of study drug to the start of the next line of treatment. Note that TTNT represents a distinct endpoint to time to subsequent anti-myeloma therapy defined in the MajesTEC-1 CSR, which includes radiotherapy and does not include deaths due to AEs.

PFS[b]	Defined as the time from the date of first dose of teclistamab to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurred first. Relapse from CR is not considered as disease progression. Patients without any post-baseline disease assessment will be censored at the date of first dose of study intervention.
≥ VGPR	Defined as the proportion of patients who achieved a ≥VGPR response according to the IMWG criteria, during or after the study intervention but before the start of subsequent anti-myeloma therapy.
≥CR	Defined as the proportion of patients achieving CR or sCR according to the IMWG response criteria, during or after the study intervention but before the start of subsequent anti-myeloma therapy.
sCR	Defined as the proportion of patients achieving sCR according to the IMWG response criteria, during or after the study intervention but before the start of subsequent anti-myeloma therapy.
Percentage of patients with negative MRD	Defined as the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} at any timepoint after initial dose of teclistamab and before disease progression or starting subsequent therapy. MRD positive patients include patients of which all tested samples were found to be MRD positive or ambiguous. Patients with missing or unevaluable MRD status will be grouped separately
Change from baseline in HRQoL as measured by EORTC QLQ-C30	The EORTC QLQ-C30 includes 30 items, with a 1-week recall, resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The instrument contains 28 items using a Likert scale with 4 response options: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much” (scored 1 to 4).
Change from baseline in HRQoL as measured by EQ 5D-5L	The EQ-5D-5L is a 5 item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analogue scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).
Change from baseline in HRQoL as measured by PGIS	The PGIS is a single item that assesses severity of the participant’s health state, on a 5-point verbal rating scale, ranging from 1 (a lot better now) to 7 (a lot worse now), at the time of completing the PRO measure. A descriptive summary of the number and percent for each response option is presented for each cycle.

[a] Occurrence and severity of AEs, SAEs and laboratory values was a primary outcome for the Phase I portion of the study. [b] For patients who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent antimyeloma therapy.
Abbreviations: AE: adverse event; ASTCT: American society for transplantation and cellular therapy; BCMA: B-cell maturation antigen; CBR: clinical benefit rate; CR: complete response; CRS: cytokine release syndrome; DoR: duration of response; EORTC: European organization for research and treatment of cancer; EQ-5D-5L: EuroQol group 5-dimension, 5 level; FLC: free light chain; GHS: global health scores; HRQoL: health related quality of life; ICANS: immune effector cell-associated neurotoxicity syndrome; IMWG: international myeloma working group; IRC: independent review committee; MM: multiple myeloma; MR: minimal response; MRD: minimal residual disease; NCI CTCAE: national cancer institute common terminology criteria for adverse events; OS: overall survival; PC: plasma cell; PD: progressive disease; PFS: progression-free survival; PGIC: patient global impression of change; PGI-S: patient global impression of severity; PR: partial response; QLQ-C30: quality of life questionnaire core-30; QLQ-MY20: quality of life questionnaire – multiple myeloma; sCR: stringent complete response; TTR: time to response; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Trial Protocol. 2021;[125] Kumar *et al.* (2016).[135]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

MajesTEC-1 was assessed for risk of bias using the modified Downs and Blacks checklist for non-randomised trials,[136] based on published sources where possible (Moreau 2022 and EHA 2023),[112, 113] but was supplemented by information provided in the protocol. This modified checklist contained 27 questions, covering the concepts of study reporting, external validity, bias, confounding, and power. Overall, the study scored as 'good' with a total score of 21/25, meaning the trial was associated with a low risk of bias.[137] The results from the quality assessment are presented in Table 12.

Table 12: Quality assessment of MajesTEC-1 using the modified Downs and Blacks checklist

Outcomes	Score	Definition	Justification
Reporting			
Is the hypothesis /aim/ objective of the study clearly described?	1	Yes	Hypothesis and objectives were clearly reported in the study protocol.
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	Yes	All prespecified efficacy and safety outcomes were measured and reported.
Are the characteristics of the patients included in the study clearly described?	1	Yes	Demographics and baseline characteristics of enrolled patients were measured and clearly reported.
Are the interventions of interest clearly described?	1	Yes	Dosage, administration and guidance were clearly reported in the study protocol.
Are the distributions of principal confounders in each group of patients to be compared clearly described?	2	Yes	Assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis of the primary efficacy endpoint of ORR based on prespecified subgroups, including sex, age, baseline renal function, baseline hepatic function, race, number of lines prior therapy and baseline ECOG score.
Are the main findings of the study clearly described?	1	Yes	All prespecified efficacy and safety outcomes were measured and reported.
Does the study provide estimates of the random variability in the data for the main outcomes?	1	Yes	Standard deviation, standard error and 95% confidence intervals were clearly reported.
Have all important adverse events that may be a consequence of the intervention been reported?	1	Yes	All important adverse events for teclistamab, including CRS rates, were clearly reported.
Have the characteristics of patients lost to follow-up been described?	1	Yes	Patients lost to follow-up were clearly reported.

Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	0	No	No p-values were measured or reported, given MajesTEC-1 was an open-label study
External Validity			
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	0	No	MajesTEC-1 was the first in-human trial of teclistamab, and therefore some patients with significant comorbidities who may be eligible for teclistamab in UK clinical practice were excluded from the trial whilst a greater understanding of the molecule was being developed.
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	1	Yes	• Teclistamab is indicated 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 the last therapy. In UK clinical practice, it is anticipated that teclistamab would be used immediately after patients have cycled through 3 prior therapies • MajesTEC-1 was a slightly more heavily pre-treated population, with a median of 5 previous lines of therapy, but represents a TCE RRMM patient population after at least 3 prior therapies and therefore broadly can be considered generalisable to the population of patients who would receive teclistamab in the UK
Were the staff, places, and facilities where the patients were treated, representative of the treatment most patients receive?	1	Yes	Patients were enrolled across multiple sites and locations in Europe, North America, and China, which are expected to broadly generalisable to patients with TCE RRMM being treated in the UK.
Internal Validity – bias			
Was an attempt made to blind study patients to the intervention they have received?	0	No	MajesTEC-1 was an open-label study
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	No	MajesTEC-1 was an open-label study
If any of the results of the study were based on “data dredging”, was this made clear?	1	Yes	All outcomes were pre-specified

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?	1	Yes	Censoring was applied to time-to-event outcomes (DOR, OS and PFS) based on Kaplan–Meier methodology
Were the statistical tests used to assess the main outcomes appropriate?	1	Yes	Two-sided 95% exact CI were calculated for ORR. Time-to-event endpoints, including DOR, PFS, and OS, and TTNT were evaluated using Kaplan-Meier method, and the median value and corresponding 95% CI were provided for each. MRD-negativity rate and its 2-sided 95% exact CI were calculated and TTR, PROs, and biomarker data were summarised descriptively
Was compliance with the intervention/s reliable?	1	Yes	Teclistamab was administered per protocol by qualified healthcare professionals and recorded in the eCRFs for each subject. As such, the risk of non-compliance by patients was considered low.
Were the main outcome measures used accurate (valid and reliable)?	1	Yes	All prespecified efficacy and safety outcomes were measured and reported.
Internal validity – confounding factors			
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1	Yes	MajesTEC-1 was a single-arm trial; as such, patients receiving teclistamab were recruited from the same population across multiple centres in Europe, North America and China, which are expected to broadly generalisable to patients with TCE RRMM being treated in the UK
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	Yes	MajesTEC-1 was a single arm trial, as such patients were enrolled to received teclistamab over the same recruitment period.
Were study patients randomised to intervention groups?	0	No	MajesTEC-1 was a single arm trial
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was finished?	0	No	MajesTEC-1 was an open-label study
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	No	MajesTEC-1 was a single arm trial

Were losses of patients to follow-up taken into account?	1	Yes	Losses to follow-up were clearly reported
Power			
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	Yes	To achieve >90% power to declare the ORR was higher than 30%, at least 112 subjects would need to receive RP2D. As such, the study was sufficiently powered given the sample size of n=165
Final score	**21**		

Abbreviations: CI: confidence interval ; CRS: cytokine release syndrome; DOR: duration of response; eCRF: electronic case report form; ECOG: Eastern Cooperative Oncology Group; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PRO: patient-reported outcome; R2PD: recommended Phase II dose; RRMM: relapsed and refractory multiple myeloma; TCE: triple-class exposed; TTR: time to response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of the clinical efficacy for teclistamab in TCE adult patients with RRMM

- The efficacy of teclistamab in TCE RRMM patients has been demonstrated in MajesTEC-1, a first-in-human, Phase I/II, ongoing trial. Results presented in this submission are based on the [redacted] pre-specified DCO of the trial (August 2023), with a median follow-up of 30.4 months

Teclistamab rapidly provides a high overall response rate (63.0%) among heavily pretreated patients with TCE RRMM

- The primary endpoint used in MajesTEC-1 was ORR, defined as the proportion of patients who achieved PR or better according to the IMWG criteria,[126] as assessed by IRC
- Treatment with teclistamab resulted in a high ORR in the All Treated Analysis Set (63.0%; N=165) in a disease resistant to all mainstream treatments.[105] This ORR represents the highest magnitude of clinical benefit on the ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies[124]
    - The level of responses achieved with teclistamab is only surpassed by those observed with talquetamab and CAR-T cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel, which demonstrated an ORR of 74.1%, 73% and 98%, respectively[119, 123, 138] Recent RWE studies found that the results observed in MajesTEC-1 are generalisable to clinical practice, reporting ORRs to teclistamab of 59.3% and 64% in patients with TCE RRMM in clinical practice[108]
- Responses to teclistamab were rapid, with a median time to first response and best response for patients in the All Treated analysis set in MajesTEC-1 of [redacted] months, and [redacted] months, respectively[124]
- At a median follow-up of 30.4 months, 46.1% of patients in MajesTEC-1 achieved a CR or better, 59.4% of patients achieved a VGPR or better, as assessed by IRC.[105] Overall, 46.1% of patients achieved a complete response or better (≥CR) (95% CI: [redacted]) (including 38.8% of patients achieving a stringent complete response [sCR] [95% CI: [redacted]])[105]
- Minimal residual disease (MRD) negativity was achieved by 29.1% of patients; 48 of the 56 MRD-evaluable patients (85.7%) in MajesTEC-1 achieved MRD negativity[105]

Responses to teclistamab are durable and deepen over time, with a median DOR of 24.0 months

- DOR was calculated among responders (with a PR or better response) from the date of initial documentation of a response to the date of first documented evidence of progressive disease as defined in the IMWG criteria, or death due to any cause
- Among responders, median DOR in the All Treated Analysis set was 24.0 months (95% CI: 17.0 months, NE months), indicative of a durable response[105]
- Median DOR for the 76 patients who achieved a CR or better in MajesTEC-1 was NE (95% CI: [redacted]), with a 24-month DOR rate of [redacted]
- According to a published SLR of 65 RRMM clinical trials, it was found that 10% increases in ORR, CR and DOR are predictive of incremental median OS gains of 4.6, 11.7 and 14.1 month gains, respectively.[80]

Teclistamab showed prolonged progression-free survival and overall survival outcomes, directly meeting patient preferences for an increased life expectancy

- Additional key secondary endpoints assessed during MajesTEC-1 included PFS and OS

- The median duration of PFS was 11.4 months (95% CI: 8.8, 16.4).[124] The estimated PFS rate at 12 months and 24 months was 48.8% (95% CI: [redacted]%, [redacted]%) and 34.2% (95% CI: [redacted], [redacted])
- In patients who achieved a CR or better, median PFS was NE (95% CI: [redacted] with a 24-month PFS rate of [redacted]% ([redacted], [redacted])Median OS was 22.2 months (95% CI: 15.1, 29.9), with an OS rate at 12 months and 24 months of 64.0% (95% CI: [redacted], [redacted]) and 48.9% (95% CI: [redacted], [redacted]), respectively
    - For the [redacted] patients who achieved a CR or better, median OS was NE (95% CI: [redacted]) and the 24-month OS rate was [redacted]% ([redacted], [redacted])

Teclistamab, an off the shelf immunotherapy, has demonstrated similar efficacy to the first-in-class BCMA CAR-T cell therapy idecabtagene vicleucel, which was reported to have a median OS and PFS of 19.4 months and 8.8 months, respectively.[119]**Health-Related Quality of Life**

- In their SLR, Fonseca et *al*. explored the relationship between HRQoL and clinical response and concluded that deeper treatment responses were associated with improved HRQoL in patients with MM [84]
- Teclistamab was associated with [redacted] in health-related quality of life (HRQoL) over time, as indicated by [redacted] from baseline in MM-related symptoms such as pain and fatigue, global health status, and functioning measured by:[105]
    - European Quality of Life Five Dimension Five Level Questionnaire (EQ-5D-5L) VAS score: The LS mean improvement in EQ-5D-5L VAS score from baseline to Cycle 12 in the mixed model for repeated measures was [redacted] (95% CI: [redacted], [redacted])
    - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30) score: Meaningful improvement from baseline to Cycle 12 was reported by [redacted]% of subjects for global health status, [redacted]% of subjects for physical functioning, [redacted]% of subjects for fatigue, and [redacted]% of subjects for pain score
    - Patient Global Impression of Severity (PGIS) scores: [redacted]% and [redacted]% of patients reporting severity as none or mild at Baseline – which increased to [redacted]% and [redacted]% at Cycle 6, and to [redacted]% and [redacted]% at Cycle 12

Conclusions

- Treatment with teclistamab resulted in rapid, deep and durable response rates and high OS and PFS rates in heavily pretreated patients with TCE RRMM in MajesTEC-1, corresponding to clinically meaningful improvements in patient's HRQoL and prolonged survival. This directly addresses MM patient preferences for a treatment which provides a longer duration of response, increased life expectancy and improved quality of life.
- The ESMO Magnitude of Clinical Benefit Scale for Hematological Malignancies (ESMO-MCBS) form 3 for single-arm trials in orphan disease areas with ORR as the primary endpoint grades the potential magnitude of clinical benefit of teclistamab as a grade 4, indicating substantial clinical benefit. This further demonstrates the significant clinical benefit teclistamab can offer patients with TCE RRMM in UK clinical practice[107]

Efficacy results for the All Treated Analysis Set from the latest DCO (August 2023) of MajesTEC-1 are provided in Sections B.2.6.1−B.2.6.8 below.

Summary of MajesTEC-1 DCOs

A summary of the DCOs from MajesTEC-1 is provided in Table 13. Regulatory approval for teclistamab was based on data from the interim March 2022 DCO.[139] Efficacy and safety data presented in this submission are based on the latest DCO (August 2023) of MajesTEC-1. As seen in Table 13, the efficacy outcomes from MajesTEC-1 have demonstrated consistency over time, with steady improvements in median OS observed, providing confidence in the stability of the long-term efficacy of teclistamab.

Table 13: MajesTEC-1 efficacy outcomes over time

Data cut	Median follow-up (months)	ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
September 2021	7.2	62.0 (53.7, 69.8)	12.5 (8.8, NE)	NR
March 2022	14.1	63.0 (52.2, 70.4)	11.3 (8.8, 17.1)	18.3 (15.1, NE)
January 2023	[redacted]	63.0 [redacted]	11.3 (8.8, 16.4)	21.9 (15.1 to NE)
August 2023 (latest DCO)	30.4	63.0 ([redacted])	11.4 (8.8, 16.4)	22.2 (15.1, 29.9)

Abbreviations: NE: not evaluable; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report;[105] MHRA. Teclistamab Summary of Product Characteristics[27]

B.2.6.1 ORR (primary endpoint)

The primary endpoint of MajesTEC-1 was ORR, defined as the proportion of patients who achieved PR or better according to the IMWG criteria, as assessed by the independent review committee (IRC).[135] The primary endpoint was met in MajesTEC-1, with an overall response by IRC assessment experienced by the majority of patients; at a median follow-up of 30.4 months, teclistamab was associated with an ORR of 63.0% (95% CI: [redacted]%, [redacted]%) in the All Treated Analysis Set (N=165).[105] An overview of response rates and follow-up based on IRC assessment of patients in the All Treated Analysis Set is presented in Table 14 and

Figure 11 below.

Treatment with teclistamab was associated with deep responses in those who achieved a response – a complete response or better (≥CR) was reported in 46.1% of patients, with 38.8% of patients achieving a sCR and 7.3% of patients achieving a CR.[105] A further 13.3% of patients experienced a VGPR, resulting in a VGPR or better rate of 59.4% in the All Treated Analysis Set.

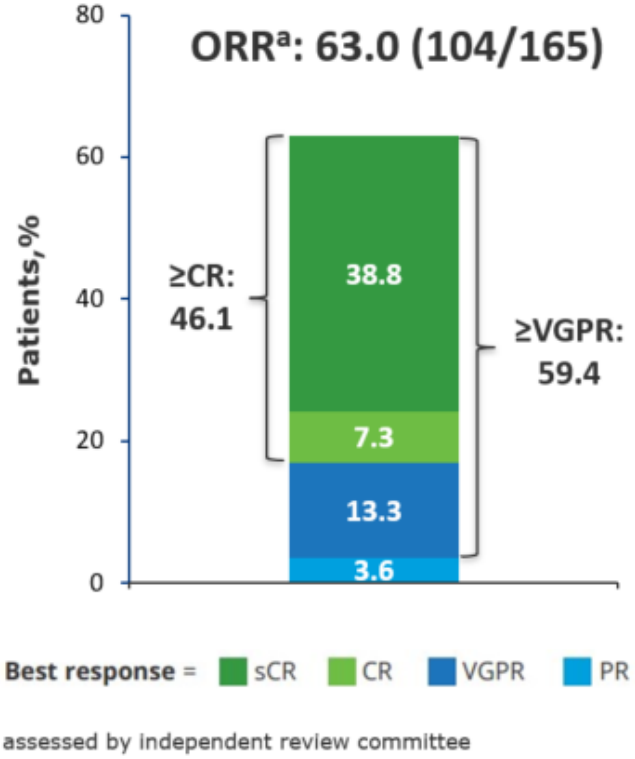
Most responses occurred early (by the time of the start of Cycle 2) and deepened over time.[124] Results from previous DCOs of MajesTEC-1 further demonstrate the deepening of responses with teclistamab treatment over time, with a consistent increase in the percentage of patients achieving a CR or better observed ([redacted]%, 39.4%, 45.5% and 46.1% of patients achieving ≥CR in the September 2021, March 2022, January 2023 and the [redacted] August 2023 DCO, respectively). Time to response data are presented in Section B.2.6.3.[105, 112, 130]

Table 14: Response rates of patients in the All Treated Analysis Set

Response rates, n (%, 95% CI)	Total N=165	
	n (%)	95% CI
ORR	104 (63.0%)	[redacted]
≥VGPR (sCR + CR + VGPR)	98 (59.4%)	[redacted]
≥CR (sCR + CR)	76 (46.1%)	[redacted]
sCR	64 (38.8%)	[redacted]
CR	12 (7.3%)	[redacted]
VGPR	22 (13.3%)	[redacted]
PR	6 (3.6%)	[redacted]
MR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]

Abbreviations: CR: complete response; MR: minimal response; ORR: overall response rate; PD: progressed disease; PR: partial response; sCR: stringent complete response; SD: standard deviation: VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 11: Response outcomes based on IRC assessment; All Treated Analysis Set



Abbreviations: CR: complete response; IRC: independent review committee; ORR: overall response rate; PR: partial response; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Clinical significance of achieving deep responses

The importance of achieving deep responses should not be overlooked. Based on the IMWG response criteria for MM, for the 38.8% of patients who have achieved an sCR with teclistamab, there are no longer any detectable MM cells in the bone marrow, and all soft tissue plasmacytomas have disappeared.[140] Furthermore, a recent SLR explored the relationship between HRQoL and clinical response and concluded that deeper responses were associated with improved HRQoL in patients with MM.[84] It is therefore also anticipated that the depth of response would have a significant impact on how people perceive their future prospects, with patients achieving deeper responses expected to be more hopeful about their future prognosis.

As previously detailed in Section B.1.3.3, OS has been found to be statistically significantly correlated with depth and duration of response, with a SLR of 65 RRMM clinical trials estimating that 10% increases in ORR and CR predict incremental median OS gains of 4.6 and 11.7 months, respectively.[80] The ORR demonstrated with teclistamab treatment also offers 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.[107]

Therefore, the high and deep response rates observed in MajesTEC-1 and the corresponding improvement in PFS and OS demonstrate the benefit that teclistamab, with its novel mechanism of action, can bring to TCE RRMM patients in whom both response rates and depth of responses are typically low.

The level of responses achieved with teclistamab have only been surpassed by those observed for talquetamab and the CAR-T cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel.[119, 138] However, teclistamab offers the advantage of being significantly easier to administer as an off-the-shelf BCMA-directed treatment option compared to CAR-T cell therapies.[119]

B.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 the All Treated Analysis Set is presented in Table 15.

Among responders, median DOR in the All Treated Analysis set was 24.0 months (95% CI, 17.0 months, NE months). The Kaplan–Meier (KM) estimate of maintenance of response for at least 6 months was 90.3% (95% CI, [redacted]%, [redacted]%).[124] The probabilities of patients remaining in response at 12 months and 24 months were 69.9% ([redacted]%, [redacted]%) and 50.1% ([redacted]%, [redacted]%) respectively.[124] A KM curve showing the change in DoR over time, based on IRC assessment are provided in Figure 12 below.

For those who achieved a CR or better, DOR was improved in comparison to patients who had not achieved CR or better, with numerically higher percentages of response at all timepoints at the time of the latest DCO.[124] The median DOR was NE (95% CI: [redacted]) the 25th percentile DOR for patients who achieved a CR or better was [redacted] months (95% CI: [redacted], [redacted]). In comparison with all responders, where the 25th percentile DOR was [redacted] months (95% CI: [redacted], [redacted]), the extended DORs for patients who achieved a CR or better demonstrates the long-term benefit of teclistamab in those who achieve the best responses to treatment. A figure presenting the KM data for DOR by CR or better for the August 2023 DCO is not yet available – a KM curve for DOR in patients who achieved a CR or better, in addition to the overall population is presented in Figure 13, based on data from the January 2023 DCO.

The combination of a high ORR and DOR observed with teclistamab is anticipated to provide a deep and prolonged treatment benefit to patients, which in turn would lead to stable or improved quality of life in TCE RRMM patients who generally achieve poor outcomes with current treatments.[11]

Table 15: Duration of response in patients in the All Treated Analysis Set

Duration of response	Total CR or better population [redacted]	All Treated Analysis Set[a] [redacted]
Number of events, n (%)	[redacted]	[redacted]
Number of events censored, n (%)	[redacted]	[redacted]
6-month event-free, % (95% CI)	[redacted]	90.3 ([redacted])
9-month event-free, % (95% CI)	[redacted]	80.6 ([redacted])
12-month event-free, % (95% CI)	[redacted]	69.9 ([redacted])
18-month event-free, % (95% CI)	[redacted]	59.2 ([redacted])
24-month event-free, % (95% CI)	[redacted]	50.1 ([redacted])

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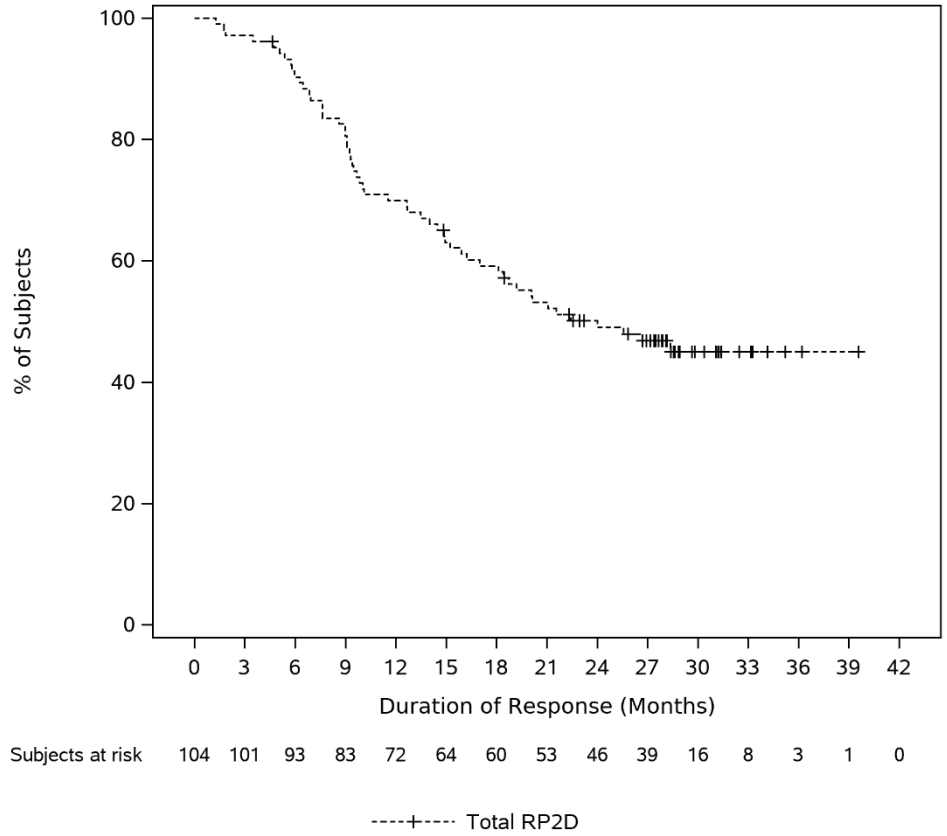
30-month event-free, % (95% CI)	[redacted]	45.0 ([redacted])
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	NE [redacted]	24.0 (17.0, NE)
75% percentile (95% CI)	[redacted]	[redacted]

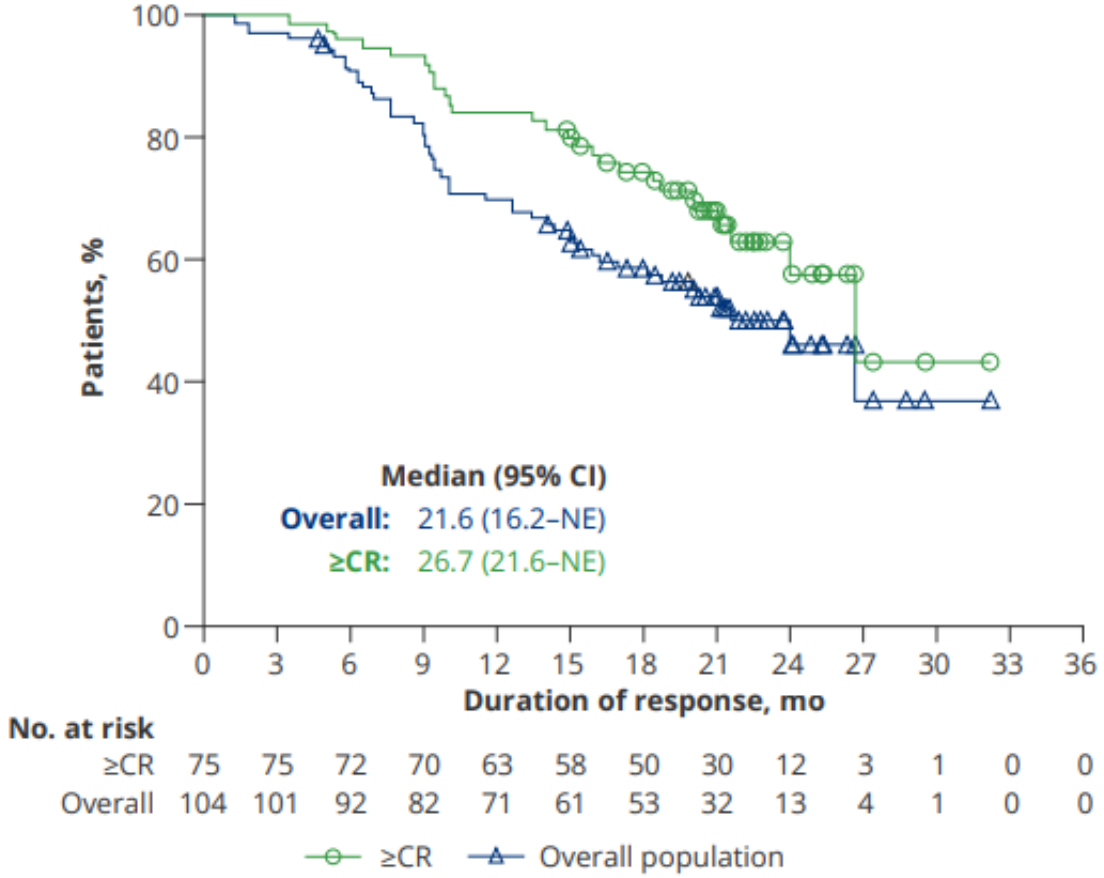
[a] [redacted] based on responders from the All Treated Analysis Set [N=165]
Abbreviations: CI: confidence interval; CR: complete response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 12: KM plot for DOR based on IRC assessment; All Treated Analysis Set



Abbreviations: DOR: duration of response; IRC: independent review committee.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 13: KM plot for DOR based on IRC assessment in patients who achieved CR or better compared with the overall population; All Treated Analysis Set (January 2023 DCO)



Abbreviations: CR: complete response; DOR: duration of response; IRC: independent review committee.
Source: Van de Donk *et al.* (2023).[141]

B.2.6.3 Time to response (secondary endpoint)

At the [redacted] August 2023 DCO, TCE RRMM patients receiving teclistamab demonstrated a short mean time to first response and mean time to best response of [redacted] months, and [redacted] months, respectively.[124] These response times illustrate the rapid onset of response triggered by the innovative mechanism of action of teclistamab. A summary of time to response for patients in the All Treated analysis set in MajesTEC-1 is provided in Table 16.

Table 16: Time to response; All Treated Analysis Set

Time to response	All Treated Analysis Set ([redacted])
Time to first response, months	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
Time to best response, months	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
Time to VGPR or better, months	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]
Time to CR or better, months	
n	[redacted]
Mean (SD)	[redacted]
Median (range)	[redacted]

Abbreviations: CR: complete response; SD: standard deviation; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.6.4 MRD negativity rate (secondary endpoint)

Minimal residual disease (MRD) was defined as the proportion of patients who achieved MRD-negative status to a threshold of 10^{-5} at any timepoint after initial dose of teclistamab 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.[105, 112]

Negativity for MRD (at a threshold of 10^{-5}) was achieved in [redacted]% of patients who achieved a CR or better, equating to 29.1% of the overall MajesTEC-1 population.[124] Notably, MRD negativity rate among patients with ≥CR improved with increased follow-up; at the time of the September 2021 DCO 41.9% of patients with ≥CR achieved MRD negativity, at the time of the March 2022 DCO 46% patients with ≥CR achieved MRD-negative status, and [redacted]% of patients with ≥CR achieved MRD negativity in the August 2023 DCO. Overall, this temporal trend towards

increased rates of MRD negativity among responding patients suggests that responses to teclistamab are durable and deepen over time.[124]

It should be noted that identification of the tumour sequence only succeeded in [redacted] patients who achieved CR or better, with calibration failing in the remaining [redacted] patients. As such, at the latest DCO (August 2023), 48 of the 56 MRD-evaluable patients (85.7%) achieved MRD negativity.[124]

B.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.[70] Additionally, results from the 2019 Myeloma UK study found that patients placed high value on 'longer remission/treatment-free periods', highlighting the importance of PFS as an outcome.[142] PFS is a surrogate marker for OS, and therefore improvements in PFS are anticipated to correlate to improvements in OS, as demonstrated in Section B.2.6.7 below.[143]

After a median follow up of 30.4 months, the median PFS was 11.4 months (95% CI, 8.8, 16.4).[105] The estimated PFS rate at 12 months and 24 months was 48.8% (95% CI: [redacted]%, [redacted]%) and 34.2% (95% CI: [redacted], [redacted]), respectively.[105] A summary of PFS results in the All Treated Analysis Set is provided in Table 17 and a Kaplan-Meier (KM) plot for PFS is presented in Figure 14.

Patients who initially responded to teclistamab are shown to achieve a stable period of progression-free survival which appears to begin plateauing towards the later part of the KM curves, compared to non-responders who demonstrated a higher rate of progression or death within the first two months of treatment.[105] The steep drop in PFS observed in non-responders highlights the poor prognosis of TCE patients in current clinical practice.[105] Clinical experts hypothesised that the patients who do not respond to teclistamab are likely to represent patients who exhibit exhausted T-cell phenotype immune profiles[144] and would face particularly poor outcomes, given the high risk nature of a heavily pre-treated RRMM population (see Section B.2.3.3).

By definition, the median PFS is therefore highly influenced by those patients who did not respond to teclistamab and does not capture the potential for long-term PFS benefits for those patients who do experience deep and durable responses to teclistamab. For the 46.1% of patients who achieved a CR or better, median PFS was not reached (NE ([redacted])). The 25th percentile PFS for patients who achieved a CR or better was [redacted] months (95% CI: [redacted], [redacted]). In comparison, for all patients in the All Treated Analysis set the 25th percentile PFS was just [redacted] months (95% CI: [redacted], [redacted]). The high 25th percentile PFS for patients who achieved a CR or better demonstrates the significant long-term benefit of teclistamab in those who respond to treatment. A figure presenting the KM data for PFS by CR or better for the August 2023 DCO is not yet available – a KM curve for PFS in patients who achieved a CR or better, in addition to the overall population is presented in Figure 13, based on data from the January 2023 DCO.

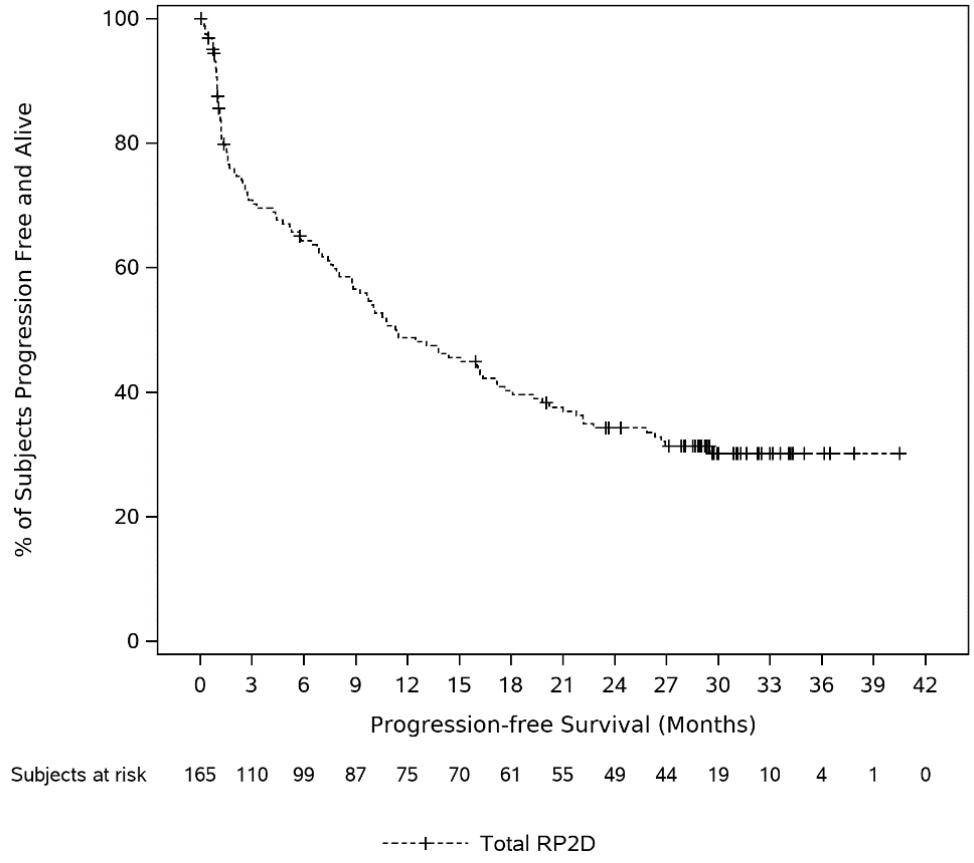
Table 17: Progression-free survival based on IRC assessment; All Treated Analysis Set

PFS Results	Total CR or better population	All Treated Analysis Set

	[redacted]	N=165
Number of events, n (%)	[redacted]	107 (64.8%)
Number of events censored, n (%)	[redacted]	58 (35.2%)
6-month PFS rate, % (95% CI)	[redacted]	64.4 [redacted]
9-month PFS rate, % (95% CI)	[redacted]	56.6 [redacted]
12-month PFS rate, % (95% CI)	[redacted]	48.8 [redacted]
18-month PFS rate, % (95% CI)	[redacted]	40.3 [redacted]
24-month PFS rate, % (95% CI)	[redacted]	34.2 [redacted]
30-month PFS rate, % (95% CI)	[redacted]	30.1 [redacted]
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	NE ([redacted])	11.4 (8.8, 16.4)
75% percentile (95% CI)	[redacted]	[redacted]

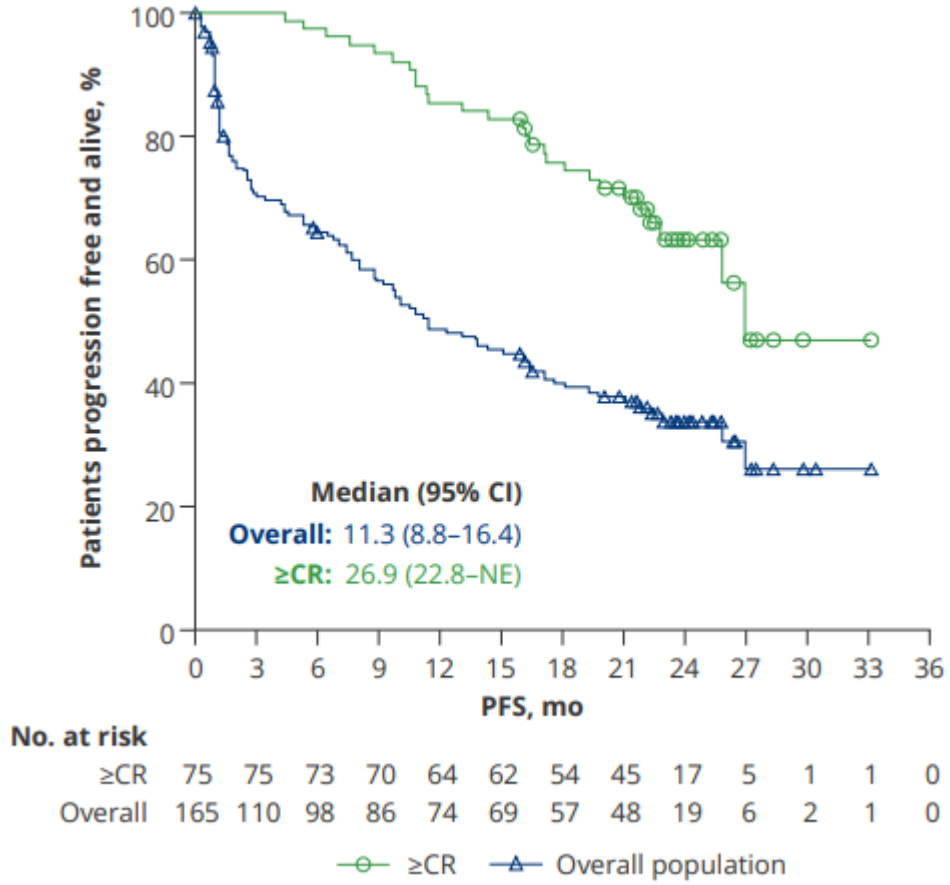
Abbreviations: CI: confidence interval; CR: complete response; IRC: independent review committee; PFS: progression-free survival.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 14: KM plot for PFS based on IRC assessment; All Treated Analysis Set



Abbreviations: IMWG: international myeloma working group; IRC: independent review committee; KM: Kaplan Meier; PFS: progression-free survival; RP2D: recommended Phase II dose.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 15: KM plot for PFS based on IRC assessment in patients who achieved a CR or better compared to the overall population; All Treated Analysis Set (January 2023 DCO)



Abbreviations: IRC: independent review committee; KM: Kaplan Meier; PFS: progression-free survival.
Source: Van de Donk *et al.* (2023).[141]

As discussed in Section B.2.3.3, clinical experts noted that due to the population of patients in MajesTEC-1 being more heavily pre-treated than patients in UK clinical practice, efficacy data from MajesTEC-1 are likely to represent a conservative estimate of the clinical benefit of teclistamab. Data from MajesTEC-1 support this; median PFS was found to be significantly higher at [redacted] months (95% CI: [redacted], [redacted]) in patients who had received ≤3 prior lines of therapy, which is more aligned with the population who would receive teclistamab in UK clinical practice.

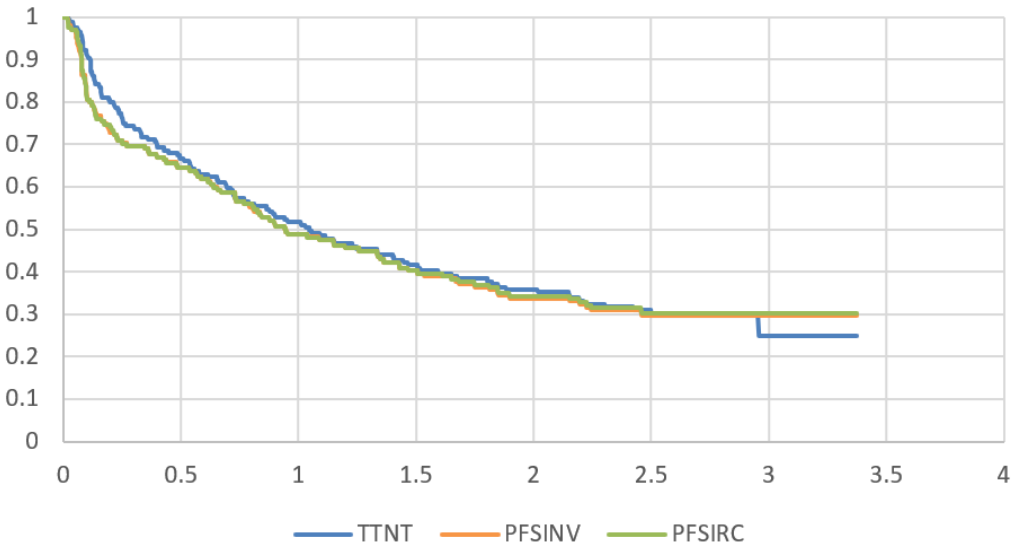
B.2.6.6 Time to Next Treatment (exploratory endpoint)

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

At the time of the August 2023 DCO, subsequent anti-myeloma therapy was reported for [redacted] patients ([redacted]), with a median time to next treatment of 12.58 months (95% CI: 8.71, 17.38).[105] As demonstrated in Figure 16, TTNT and PFS results in MajesTEC-1 were highly consistent, (median PFS of 11.4 months (95% CI: 8.8, 16.4)), and the KM curves for TTNT and PFS

demonstrated a very similar trajectory over time. Together, this supports the use of TTNT as a proxy for PFS in the ITC (see Section B.2.9).

Figure 16: TTNT and PFS (assessed by the IRC) in MajesTEC-1



Abbreviations: IRC: Independent Review Committee; PFS: progression-free survival; TTNT: time to next treatment.

B.2.6.7 Overall survival (secondary endpoint)

At the time of the [redacted] August 2023 DCO, 57% of OS events had occurred, with a median OS of 22.2 months (95% CI, 15.1 to 29.9).[105] A summary of OS is provided in Table 18.

A KM plot illustrating the OS with teclistamab in MajesTEC-1 is depicted in Figure 17. The OS rate at 12 months and 24 months were 64.0% and 48.9%, respectively.[124] The decline in OS can generally be seen to steadily decrease over time likely reflecting the subset of patients who have experienced the deepest responses to teclistamab and subsequently have the potential to experience a long-term survival benefit. The durable responses and potential for long-term survival with teclistamab were also highlighted by UK clinical experts during interviews conducted by Janssen in December 2023.[83]

For those who achieved a CR or better, the median OS was not reached (NE (95% CI: [redacted]), and [redacted] of these patients were still alive after 2 years. The benefits of a CR response are highlighted by comparison of the 25th OS percentiles (the point at which 25% of patients had died) - the 25th percentile OS for patients who achieved a CR or better was [redacted] months (95% CI: [redacted], [redacted]), compared to [redacted] months (95% CI: [redacted], [redacted]) in the All Treated Analysis set. This comparison highlights the potential for substantial long-term survival benefit for those patients who experience the best responses with teclistamab. This benefit is not fully reflected in the overall median OS estimate from MajesTEC-1 of 22.2 months.[105] As the KM data for OS by CR or better for the August 2023 DCO is not yet available, a KM curve for OS in patients who achieved a CR or better, in addition to the overall population is presented in Figure 18, based on data from the January 2023 DCO.

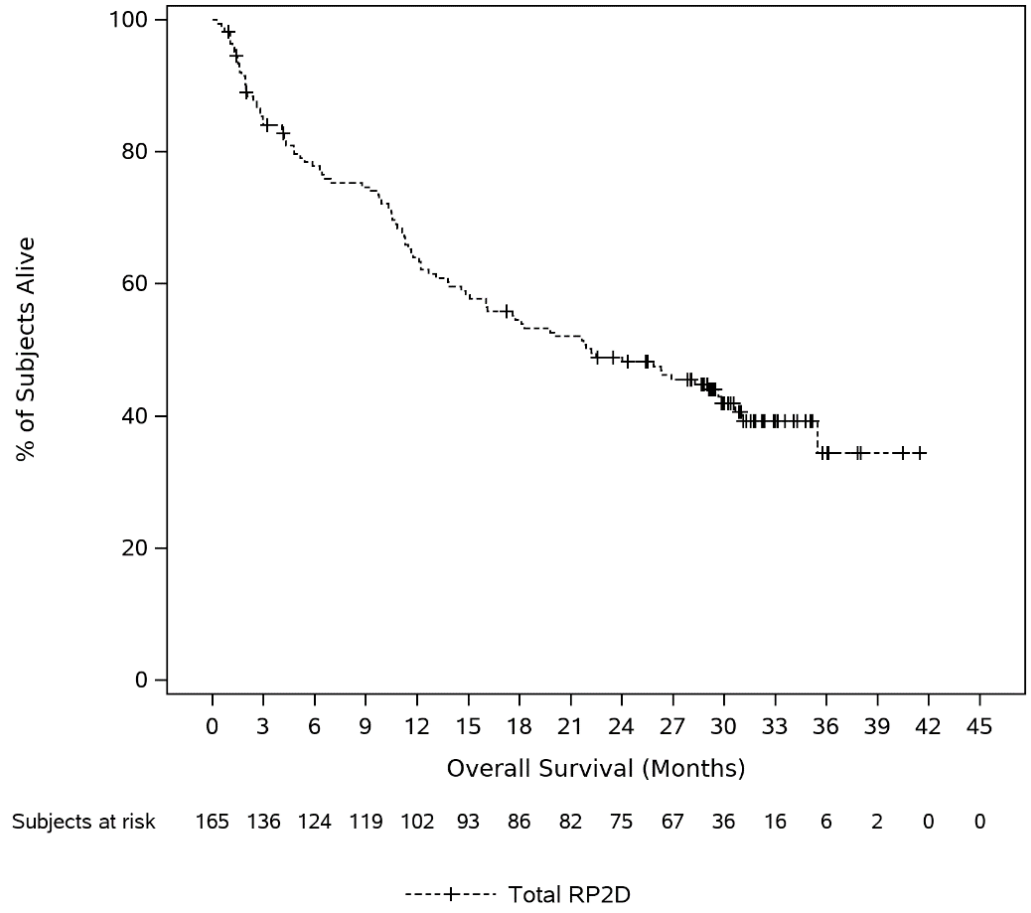
Collectively, these findings suggest that the improvements observed in ORR (Section B.2.6.1) and PFS (Section B.2.6.5) correlate with improved survival outcomes in patients with TCE RRMM treated with teclistamab. Thus, this illustrates the substantial clinical benefit offered by the novel mechanism of action of teclistamab to a patient population currently facing a very poor prognosis.[11, 145]

Table 18: Overall survival in patients in the All Treated Analysis Set

Overall Survival	Total CR or better population [redacted]	All Treated Analysis Set N=165
Number of events, n (%)	[redacted]	94 (57.0%)
Number of censored (%)	[redacted]	71 (43.0%)
6-month OS rate, % (95% CI)	[redacted]	77.8 [redacted]
9-month OS rate, % (95% CI)	[redacted]	74.7 [redacted]
12-month OS rate, % (95% CI)	[redacted]	64.0 [redacted]
18-month OS rate, % (95% CI)	[redacted]	54.6 [redacted]
24-month OS rate, % (95% CI)	[redacted]	48.9 [redacted]
30-month OS rate, % (95% CI)	[redacted]	41.9 [redacted]
Median KM estimate, months (95% CI)		
25% percentile	[redacted]	[redacted]
Median	NE ([redacted])	22.2 (15.1, 29.9)
75% percentile	[redacted]	[redacted]

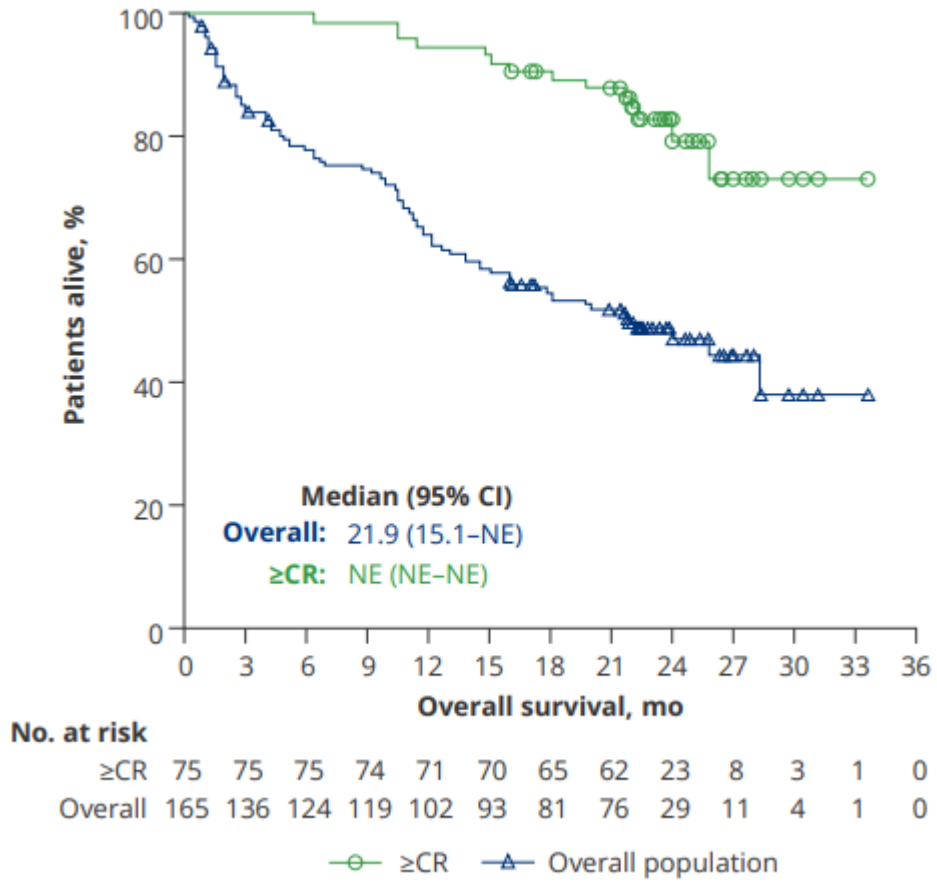
Abbreviations: CI: confidence interval; KM: Kaplan Meier; OS: overall survival.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 17: KM plot for overall survival; All Treated Analysis Set



Abbreviations: KM: Kaplan Meier; RP2D: recommended phase II dose.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 18: KM plot for OS based on IRC assessment in patients who achieved a CR or better compared to the overall population; All Treated Analysis Set (January 2023 DCO)



Abbreviations: CR: complete response; IRC: independent review committee; OS: overall survival; PFS: progression-free survival.
Source: Van de Donk *et al.* (2023).[141]

Potential impact of COVID-19 and heavily pre-treated nature of the patient population on OS

As discussed in Section B.2.10, 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. Additionally, as noted in Section B.2.6.5, the heavily pre-treated nature of the patient population may further exacerbate the conservative nature of these OS estimates compared to the patient population who would receive teclistamab in UK clinical practice.

B.2.6.8 Patient-reported outcomes

HRQOL measures and baseline scores

HRQoL was assessed in patients in Cohort A of Phase II of MajesTEC-1 (see Section B.2.3.1). HRQoL was assessed at baseline and then every other cycle until end of treatment using the following patient reported outcome (PRO) instruments: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30), the EuroQol Five Dimensions Five Level (EQ-5D-5L), and the Patient Global Impressions-Severity (PGI-S). The post-treatment follow-up phase of MajesTEC-1 started after the end of treatment visit and assessed PROs approximately every 16 weeks until the end of study, unless the patient had died, was lost to follow-up, or withdrew consent.[125]

A detailed discussion of each questionnaire and the improvement in PROs over time seen in patients treated with teclistamab is provided below.[105] This improvement in HRQoL demonstrates how the rapid, deep and durable responses seen with teclistamab have translated to enhancements in HRQoL in this patient population who generally experience the worst HRQoL reported for all blood cancers (See Section B.1.3.3).[105]

The EORTC QLQ-C30 questionnaire was used to assess patient functioning and symptoms, such as pain, fatigue, and physical functioning, as well as overall HRQoL. Scores range from 0 to 100, with higher scores indicative of better health on global health status (GHS) and functional scales, and greater symptom severity on symptom scales. In total, [redacted]% of patients from Cohort A completed the EORTC QLQ-C30 questionnaire at baseline, reporting poor overall GHS at baseline, with a mean score of [redacted]. RRMM was also reported to have a particularly burdensome impact on physical and role functioning as well as pain and fatigue.[105]

The EQ-5D-5L is a generic measure of health status. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analogue scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. In total, [redacted]% of patients from Cohort A completed the EQ-5D-5L questionnaire at baseline, reporting poor overall health status scores at baseline, with a mean score of [redacted].[105]

The PGI-S is a single item that assesses severity of the patient’s health state, on a 5-point verbal rating scale, at the time of completing the PRO measure. Response on the PGI-S was used as an anchor to determine meaningful change thresholds and interpretation of results for the EORTC QLQ-C30. In total [redacted]% of patients from Cohort A completed the PGI-S questionnaire at baseline, with [redacted]% and [redacted]% of patients reporting disease severity as none or mild.[105]

HRQOL with teclistamab treatment

Approximately [redacted] of the patients reported [redacted] in pain and fatigue symptoms from baseline through the first twelve cycles of teclistamab monotherapy. This definition of meaningful improvement is based on Cocks *et al.* (2008).[146] The proportion of patients with a [redacted] in these subscales generally increased over time, with the

majority of patients reporting [redacted] across EORTC QLQ-C30 symptom scores at Cycles 10 through 12, as illustrated in Table 19 below.[105]

Patients also exhibited [redacted] in overall health (as measured by GHS) and physical and role functioning with teclistamab. [redacted] from baseline to Cycle 12 was reported by [redacted]% of subjects for global health status, [redacted]% of subjects for physical functioning, [redacted]% of subjects for fatigue, and [redacted]% of subjects for pain score (Figure 19 and Figure 20).[105] Patients in the 2019 Myeloma UK study reported that fatigue and tiredness have the biggest impact on daily life, while mobility, daily activities, pain and discomfort all ranked highly as factors impacting the lives of patients with MM.[76] Therefore, the [redacted] seen with teclistamab treatment are directly aligned with patient preferences.

A summary of the [redacted] in EQ-5D-5L scores from baseline in MajesTEC-1 is presented in Figure 21 below. At baseline, patients reported a mean visual analogue scale (VAS) score of [redacted] (SD: [redacted]), which remained consistent across initial treatment with teclistamab (Cycle 2 Day 1 mean VAS: [redacted] [SD: [redacted]]). [redacted] in VAS scores were first observed at the initiation of Cycle 4, with a mean change from baseline of [redacted] (SD: [redacted]), and continued to [redacted] with prolonged therapy, with a mean change from baseline to Cycle 12 of [redacted] (SD: [redacted]). In alignment with these findings, the median time to [redacted] in VAS score was [redacted] months.[105]

For PGIS scores, [redacted]% and [redacted]% of patients reporting severity as none or mild at baseline – which increased to [redacted]% and [redacted]% at Cycle 6 and [redacted]% and [redacted]% at Cycle 12 (Figure 22). This demonstrates an [redacted] in disease severity with treatment with teclistamab.[105]

These results indicate that teclistamab results in [redacted] in HRQOL over time, indicated by [redacted] from baseline in important MM-related symptoms such as pain, fatigue, global health status and functioning. TCE RRMM is generally associated with particularly poor HRQoL, which increases with each successive LOT, highlighting the key unmet need for an effective novel treatment option for this patient population. Additionally, as noted in Section B.1.3.3, patients reported pain and fatigue as amongst the worst effects of MM, therefore highlighting the benefit of teclistamab in [redacted] these symptoms.

Table 19. Meaningful improvement in EORTC QLQ-C30 subscales from baseline in MajesTEC-1 (literature-based approach); Phase II Cohort A, All Treated Analysis Set[a]

EORTC QLQ-C30 Subscale	Cycle 2 Day 1		Cycle 4 Day 1		Cycle 6 Day 1		Cycle 8 Day 1		Cycle 10 Day 1		Cycle 12 Day 1		EOT	
	N	AMC, n (%)	N	AMC, n (%)	N	AMC, n (%)	N	AMC, n (%)	N	AMC, n (%)	N	AMC, n (%)	N	AMC, n (%)
Phase II Cohort A in All Treated Analysis Set	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-
Symptom Scales														
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleep disturbances	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Functioning Scales														
Global health status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Physical functioning	[redacted]													
Role functioning	[redacted]													
Social functioning	[redacted]													

[a] Meaningful improvements are defined based on the literature-based approach
Abbreviations: AMC: achieved meaningful change; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item; EOT: end of treatment.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 19: Meaningful improvements in EORTC QLQ-C30 Symptom Scales for Fatigue and Pain over Time in MajesTEC-1 (Phase II Cohort A; All Treated Analysis Set)

Abbreviations: EOT: end-of-treatment.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Table 20: Total number of patients at each timepoint for measures of meaningful improvements in EORTC QLQ-C30 scores for fatigue and pain

Total number of patients	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 6 Day 1	Cycle 8 Day 1	Cycle 10 Day 1	Cycle 12 Day 1	EOT
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EOT: end of treatment.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 20: Meaningful Improvements in EORTC QLQ-C30 Functioning Scales for Global Health Status, Physical Functioning and Role Functioning over Time in MajesTEC-1 (Phase II Cohort A; All Treated Analysis Set)

Abbreviations: EOT: end of treatment.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Table 21: Total number of patients at each timepoint for measures of meaningful improvements in EORTC QLQ-C30 scores for Global Health Status, physical functioning and role functioning

Total number of patients	Cycle 2 Day 1	Cycle 4 Day 1	Cycle 6 Day 1	Cycle 8 Day 1	Cycle 10 Day 1	Cycle 12 Day 1	EOT
Global Health Status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EOT: end of treatment.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 21: Mean values for EQ-5D-5L VAS score over time (Phase II Cohort A; All Treated Analysis Set)

Abbreviations: EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level; VAS: visual analogue scale.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 22: Patient's Global Impression of Multiple Myeloma Disease Severity Responses in MajesTEC-1 (Phase II Cohort A; All Treated Analysis Set)

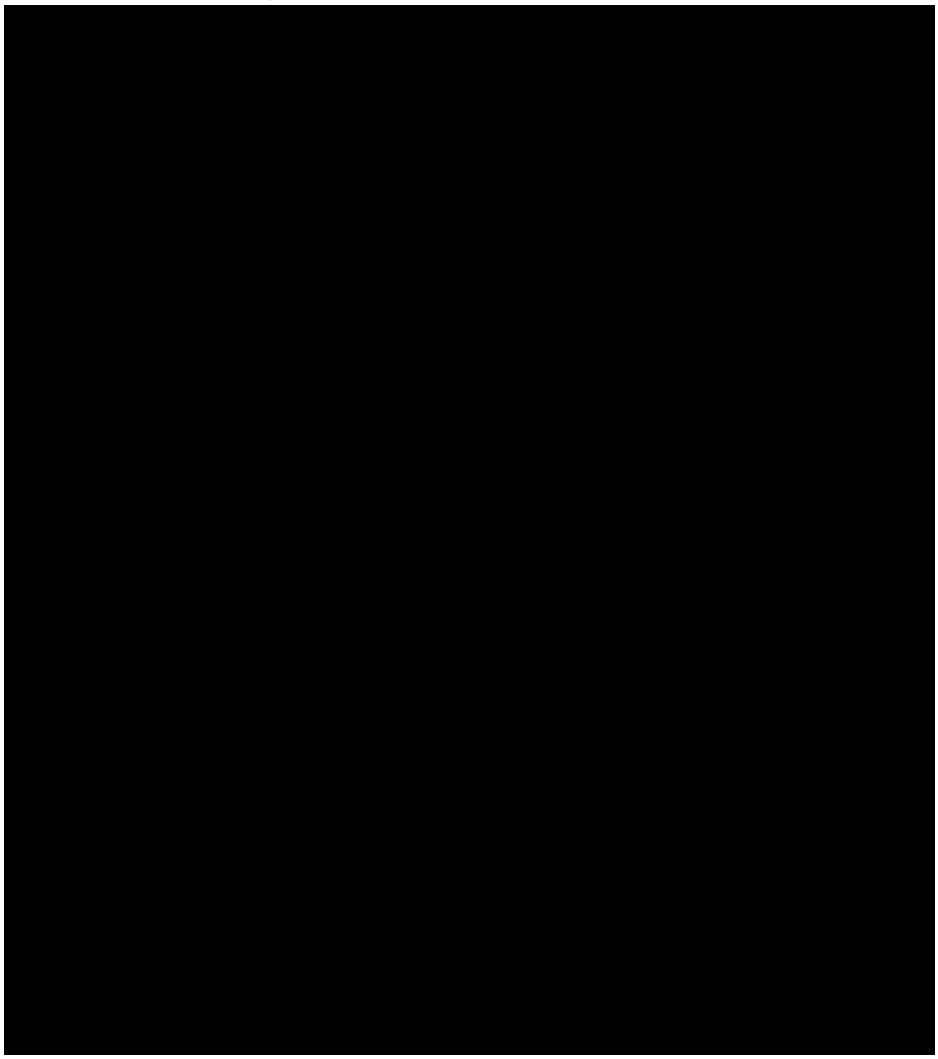
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.7 *Subgroup analysis*

An overview of the subgroup analyses of ORR in MajesTEC-1 study is presented in Figure 23, Figure 24 and Figure 25 below for baseline disease characteristics, baseline demographic characteristics and number of lines of prior therapies, respectively.

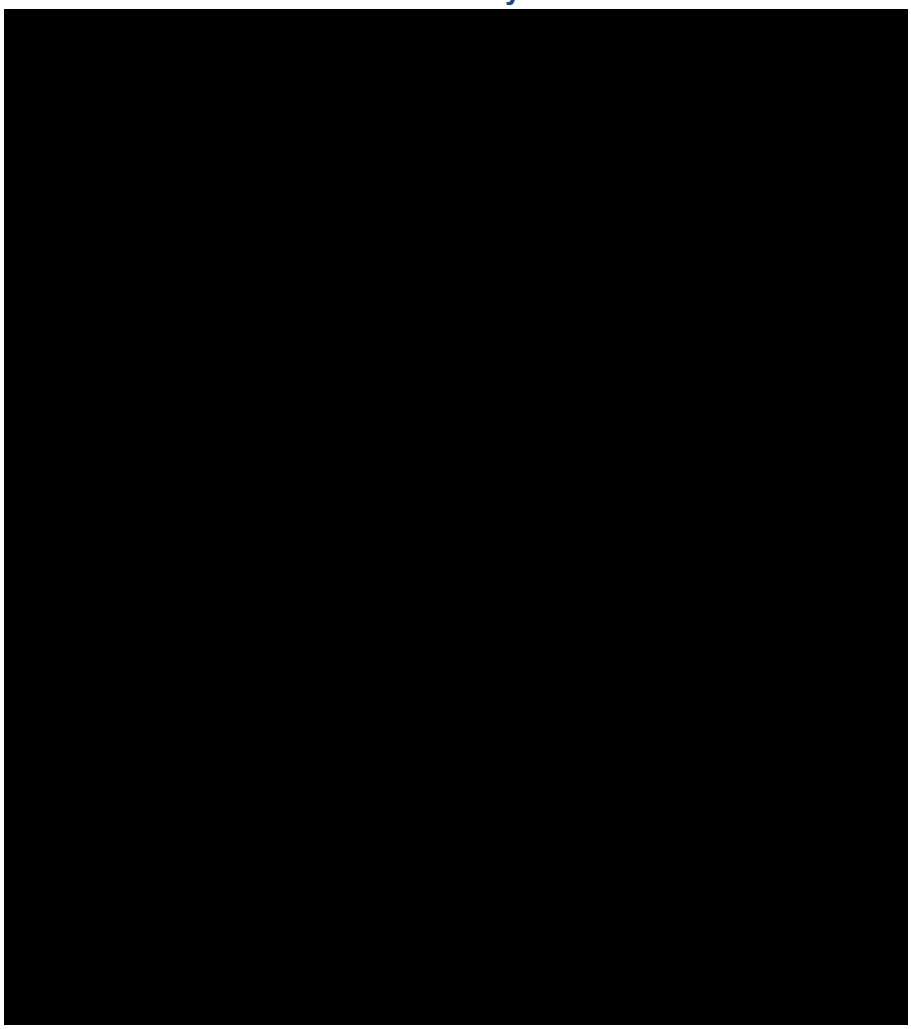
At 30.4 months median follow-up at the [redacted] August 2023 DCO, subgroup analyses demonstrated that the ORR was consistent among patients across the subgroups stratified by refractoriness to prior therapies and BCMA expression.[105] Whilst numerical differences in ORR were observed in the subgroups versus the overall population, none of these reached statistical significance with the exception of ISS stage III and extramedullary plasmacytomas ≥1.

Figure 23: Forest plot of ORR in subgroup analyses of baseline disease characteristics in the All Treated Analysis Set



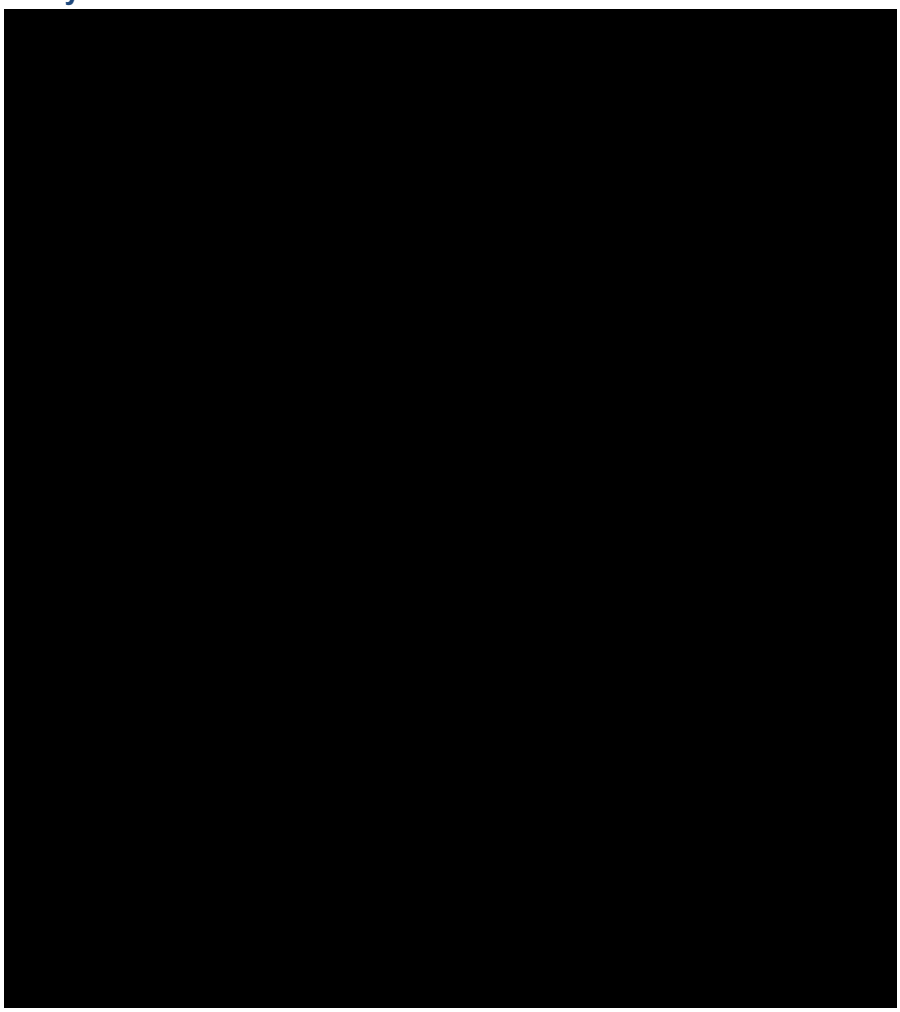
Abbreviations: ORR: overall response rate.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 24: Forest plot of ORR in subgroup analyses of baseline demographic characteristics in the All Treated Analysis Set



Abbreviations: ORR: overall response rate.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 25: Forest plot of ORR in subgroup analyses of prior therapies in the All Treated Analysis Set



Abbreviations: ORR: overall response rate.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.8 *Meta-analysis*

As MajesTEC-1 is the only trial for teclistamab in the population of relevance to this indication and due to the single-arm nature of the trial, no meta-analysis was possible.

B.2.9 *Indirect and mixed treatment comparisons*

An indirect treatment comparison (ITC) using IPD from the UK RW TCE cohort study and MajesTEC-1 was required and utilised an ATC IPTW approach (in base case), resulting in a MajesTEC-1 cohort that was highly matched to the UK RW TCE population

- There are no published clinical trial data for PomDex for patients with TCE RRMM who have received at least three prior therapies. As such, aligned with the accepted approach in TA889, Janssen gathered real-world data for patients with TCE RRMM receiving PomDex in UK clinical practice.
- In the base case ITC approach, the MajesTEC-1 cohort was reweighted to match the UK RW TCE cohort study via inverse probability of treatment weighting (IPTW) in line with NICE TSD 17[109]. This IPTW approach adjusted for five key prognostic variables (refractory status, number of prior lines of therapy, months since diagnosis, age and ECOG score) and resulted in a high degree of overlap between the MajesTEC-1 cohort and the UK RW TCE population (i.e., all SMD < 0.2)

The ITC demonstrated that MajesTEC-1 shows consistent clinical benefit (PFS and OS) of teclistamab versus PomDex

- Treatment with teclistamab resulted in a statistically significant and clinically meaningful improvement in PFS [based on TTNT as a proxy] (HR: 0.56; 95% CI: 0.40, 0.79), translating to an improvement in median PFS of 5.36 months (12.39 versus 7.03 months; representing a 76.2% increase). Thus, treatment with teclistamab reduces the risk of progression or death by 44% compared to PomDex.
- The prolonged PFS translated to a statistically significant and clinically meaningful improvement in OS (HR: 0.52; 95% CI: 0.36, 0.74) i.e., 48% reduction in the risk of death, and an improvement in median OS of 12.43 months (22.21 versus 9.78 months; representing a 2.27-fold increase)
- These results were consistent across an extensive range of sensitivity analyses (which varied the IPTW approach and number of prognostic variables adjusted for).
- Furthermore, the base case analysis produced the most conservative results of all sensitivity analyses, consequently representing the upper bound of the relative efficacy between teclistamab and PomDex.

SLR

In total, the clinical SLR identified 455 studies in RRMM reporting on 218 unique studies. The full details of the methodology and results of the clinical SLR are reported in Appendix D.

No studies were identified that reported results for PomDex specifically in a patient population with TCE RRMM after at least 3 prior therapies and consequently, no studies were considered relevant for informing efficacy estimates for patients with TCE RRMM receiving PomDex. UK RW TCE cohort study

UK RW TCE RRMM cohort study

In the absence of head-to-head data, the UK RW TCE cohort study - a registry study using NHS England's (NHSE's) cancer and linked datasets available through the NCRAS – was conducted to source UK-specific data on PomDex in TCE RRMM.[145] This study was considered to represent

the most appropriate data source for PomDex to inform the comparative efficacy evidence in this submission. The main outcomes from the UK RW TCE cohort study were OS and TTNT (used as a proxy for PFS in the absence of PFS data [See Section B.2.6.6]). Patients were followed up from the initiation of their current LOT until death, embarkation (relocation outside of England) or until DCO. The most recent DCO was March 2023, which was used to inform the ITC, and the median follow-up time for the PomDex cohort was 26.0 months.

A summary of the study is presented in Table 22 and full details, including the methods, baseline characteristics and study results, are presented in Appendices D and M. NICE's preferred DataSAT RWE tool, as well as the ROBINS-I checklist providing a quality assessment of the UK RW TCE cohort study, are also provided in Appendix D. The risk of bias was estimated to be low, indicating that the ITC results are robust, albeit with unavoidable confounding bias associated with real-world registry studies like the UK RW TCE cohort study.

The UK RW TCE cohort study is highly reflective of the real-world population that is likely to receive teclistamab in UK clinical practice (see Section B.1.3.4) i.e., patients who start their first LOT after becoming TCE following at least three or more prior therapies.

Table 22: Summary of methodology of the UK RW TCE RRMM cohort study in England

Study design	A descriptive, non-interventional, cohort study designed to retrospectively track the treatment pathway and health outcomes of patients with MM using routine healthcare data.
Data sources	Several linked datasets available through the NCRAS at NHSE: • The NCRD provides a register of primary cancer diagnoses in England from 1971 to 2021[147] • The HES database provides national coverage of secondary care, including inpatient, outpatient, and accident and emergency admissions[148] • SACT contains cancer-specific systemic treatment information for NHS patients in England[149]
Study populations	General eligibility criteria: Included patients had one or more primary MM diagnosis, defined as ICD-O-3 morphology code 9732, between 1 January 2013 and 31 December 2021 in England and were aged ≥18 years at diagnosis. It was further required that patients received three or more LOTs that included a PI, an IMiD, and an anti-CD38 mAb, either alone or in combination. Patients were excluded if their MM diagnosis was identified via death certificate only, as the lack of follow-up data negates any ability to calculate treatment or survival. They were also excluded if there was no linkage to a SACT record for an ICD-10-C90 tumour, where treatment was after or up to 1 month before the first cohort-relevant diagnosis. The study included an 'overall cohort' and to be eligible for inclusion, all patients must have received at least three prior MM treatments, including a PI, an ImiD and an anti-CD38 mAb. An additional cohort, PomDex, was defined specifically to inform the NICE appraisal of teclistamab, as specified in Table 23. The overall cohort and study methodology is further described by Elsada *et al*. (2021).[11] Table 23. Study populations in UK RW TCE cohort study

		Additional eligibility criteria	**Definition of the 'index LOT'**
	Overall cohort	Patients must have initiated a new line of systemic anti-cancer therapy after meeting the general eligibility criteria, i.e., after becoming TCE following three or more prior LOTs. Note that CDF treatment data was not available in this dataset.	The first line of systemic anti-cancer therapy that follows the patient meeting all eligibility criteria.
	PomDex cohort (ECOG restricted 0−1)	Patients must have initiated a new line of PomDex therapy after meeting the general eligibility criteria and have an ECOG score at baseline of 0 or 1.	The first PomDex LOT that follows the patient meeting all eligibility criteria (this may or may not be the first LOT received after becoming eligible).
Time zero and follow-up	T^0 was defined as the start of the index LOT. Patients were followed from T^0 to the earliest of death, embarkation (relocation outside England), or March 2023.		
Outcomes	OS and TTNT [proxy for PFS due to absent PFS data] were calculated using the KM estimator: • OS failure was defined as death from any cause between T^0 and the end of follow-up • TTNT was the earliest of either a change in LOT or death within the study period Patients for both outcomes were censored on March 2023 if alive at the end of the study period, or else on the date of embarkation if they left England during the period of study.		
Subsequent therapy	Patient counts and regimen descriptions were generated for those who went on to receive one or more subsequent LOT after their index LOT within the study period.		

Abbreviations: CD38: cluster of differentiation 38; HES: hospital episode statistics; ICD-10-C90: International Classification of Diseases, Tenth Revision, code C90; ICD-O-3: International Classification of Diseases for Oncology, code 3; IMiD: immunomodulatory agent; KM: Kaplan-Meier; LOT: line of treatment; MM: multiple myeloma; mAb: monoclonal antibody; NCRAS: National Cancer Registration and Analysis Service; NCRD: National Cancer Registration Dataset; NHS: national health service; NICE: National Institute of Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PI: proteasome inhibitor; PomDex: pomalidomide in combination with dexamethasone; RRMM: relapsed or refractory multiple myeloma; SACT: Systemic Anti-Cancer Therapy dataset; T0: time zero; TCE: triple-class-exposed; TTNT: time to next treatment; UK: United Kingdom.

Data availability

Aggregate data are available for all study cohorts. In addition, row-level broadly categorised patient data that passed a K-3 anonymity check as per the Department of Health and Social Care's (DHSC) anonymisation standard for publishing health and social care data,[150] and was approved by NHSE's Caldicott Guardian, were provided for the PomDex cohort. This was to allow for adjusted comparisons with MajesTEC-1 using methods for comparative individual patient data, including adjustments for covariates to correct for bias arising from comparing treatment effects in different populations.

In total, 896 patients in the UK RW TCE cohort study received PomDex. However, unlike MajesTEC-1, the UK RW TCE cohort study did not restrict the eligible population to patients with an ECOG Performance Status (PS) of 0 or 1. Therefore, to align with the inclusion criteria of MajesTEC-1, the ITC used only the subset of patients from the registry study with an ECOG PS of 0 or 1 resulting in a final sample size of N=645 in the UK RW TCE PomDex cohort and N=165 in the MajesTEC-1 cohort (after imputation of N=214 missing values in the UK RW TCE PomDex cohort).[145]

A limitation of the UK RW TCE cohort study is that a number of prognostic variables are not routinely collected in UK clinical practice (e.g. cytogenetic profile). This restricts the variables that can be adjusted for in the ITC since certain prognostic factors reported in MajesTEC-1 were not reported in the UK RW TCE cohort study. Additionally, patients referred to palliative care (with a poorer prognosis) are not captured in the UK RW TCE cohort study, whereas there is a population of patients in UK clinical practice who receive palliative care and therefore there is a potential bias against teclistamab.

However, despite these potential limitations, this cohort of patients was used in the ITC for the cilta-cel submission and was accepted by the committee as appropriate for decision making. The Evidence Assessment Group (EAG) noted the cohort to be broadly representative of patients who would receive cilta-cel in the UK, i.e. patients with TCE RRMM, and clinical advisers to the EAG confirmed that the OS and TTNT (PFS) outcomes observed were reflective of outcomes seen in UK clinical practice.[9]

TTNT as a proxy for PFS

In the absence of data from the UK RW TCE cohort study sufficient for defining disease progression according to IMWG criteria,[151] TTNT was chosen to act as a proxy for PFS. To align the outcomes being compared, TTNT MajesTEC-1 was likewise used as a proxy for teclistamab PFS in the analysis, rather than using MajesTEC-1 PFS directly. The use of TTNT as a proxy for PFS was considered acceptable based on the following reasons:

- Clinical experts consulted during interviews conducted in December 2023 indicated that in the fourth-line setting, they would expect TTNT and PFS to overlap considerably, making TTNT an appropriate proxy for PFS.[83] Support for the considerable overlap between TTNT and PFS in this setting is provided by data obtained from MajesTEC-1 (Section B.2.6.6; Figure 16), which showed that the TTNT and PFS results from MajesTEC-1 were closely aligned.

- Real-world data from seven European countries, including the UK, showed that the median treatment-free interval between fourth- and fifth-line treatment was only 1 month.[152] Recent data from the UK reported an even shorter median treatment-free interval between these two LOTs of 0.8 months.[153] Therefore, there is unlikely to be significant bias in the PFS estimate inferred from TTNT at this stage in therapy.

- TTNT is an appropriate proxy for PFS, given the short delay in practice between progression and initiation of next treatment in the 4th and subsequent LOT setting.

B.2.9.1 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[109] – are routinely used to estimate relative treatment effects while adjusting for observed differences between populations of interest.

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.[154, 155] 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 untreated groups are balanced after weighting.

In this way, treated individuals with a lower probability of exposure receive larger weights compared to untreated individuals who receive weights equal to one. Consequently, the relative influence of the treated individuals on the comparison is increased – this weighting approach is termed ‘average treatment effect for the control (ATC)’ and was applied in the base case ITC analysis. 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 MajesTEC-1 cohort and the PomDex cohort at the index date. For the reweighting approach, the estimated PSs were used to derive weights for each patient using estimand-specific weighting formulas (presented in Appendix D).

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 B.2.9.5).[156]

Weighting approaches

There are multiple weighting approaches available using IPTW; ATC, average treatment effect (ATE) and average effect of the treatment (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 population in the UK RW TCE cohort study was considered. The UK RW TCE cohort study provides data for a UK population of patients with TCE RRMM receiving PomDex and, consequently, is directly aligned with the anticipated population of patients who would receive teclistamab in UK clinical practice. Since the UK RW TCE cohort study is considered to better represent the target population for teclistamab in the UK versus the MajesTEC-1 cohort, ATC was considered to be the most appropriate methodology for adjustment since this would enable the characteristics of the MajesTEC-1 cohort to be re-weighted to mimic those of the UK RW TCE cohort study and, therefore, the population of relevance to this submission.

UK clinical and health economic experts consulted in the preparation of this submission validated the choice of weighting;[83] it was considered appropriate to reweight the MajesTEC-1 trial population to align with the UK RW TCE patient population given the study population is directly aligned with the population who would be eligible to receive teclistamab in UK clinical practice. Furthermore, use of ATC weighting in the base case analysis is aligned to that used in the ITC for the cilta-cel submission (TA889), which was previously accepted as appropriate for decision-making by the NICE committee.[9]

To explore uncertainty surrounding the weighting method used in the base case analysis, alternative estimand weightings, including the ATT, ATO and the ATE were explored.

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

B.2.9.2 Identification of covariates

The final list of covariates for the ITC were selected based on several rounds of clinical validation meetings that the Company conducted for RRMM with multiple clinical experts in July 2022, including the previous validation exercise conducted to inform the cilta-cel submission (TA889). This list of covariates was further validated by four UK clinical experts consulted during interviews conducted in December 2023. In total, 17 potential covariates were identified of which 5 were deemed to be priority prognostic factors (Table 24).

Of the 17 variables listed, only 6 variables (refractory status, number of prior lines of therapy, months since diagnosis, age, prior stem cell transplant and ECOG PS score) had sufficient

individual patient-level data available from the UK RW TCE cohort study and thus could be adjusted for. The justifications for the absence of the other variables are described below:

- **Extramedullary plasmacytoma:** The dataset from which the variable was extracted was not considered reliable since it was not possible to classify missing data. Additionally, there is a risk that extramedullary plasmacytoma may not have been correctly recorded in HES, if it was diagnosed and treated solely in an outpatient appointment, since HES outpatients can be an unreliable dataset
- **Race:** It was not possible to obtain row-level data on the variable irrespective of anonymity check
- **Sex:** The variable was deprioritised to be able to pass the K-3 anonymity check[150]
- **ISS stage**: while ISS stage was recorded, data was missing for high proportion of patients (>65%) and thus could not be adjusted for
- **All other variables:** The variables are not available within the NHSE's datasets

Whilst it was not possible to adjust for some variables due to lack of data, additional feedback received from clinical experts highlighted that some of these factors were not considered to have strong prognostic impact in the TCE setting. In particular, it was noted that race, sex, creatinine levels and lactate dehydrogenase (LDH) levels are weak prognostic factors. Consequently, exclusion of these factors is not anticipated to substantially impact the results of the ITC analysis.

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

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

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

Company evidence submission template for teclistamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID6333]

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

B.2.9.3 Assessment of overlap

The extent of overlap between populations with respect to the six variables available in UK RW TCE cohort study was evaluated before and after adjustment. Standardised mean differences (SMDs) were used to evaluate the differences for each variable included in the analysis, with a SMD greater than 0.2 indicating a substantial difference between the populations.

Before adjustment

SMDs calculated before adjustment are presented in Table 25 while histograms of PSs are depicted in Figure 27. Compared to the PomDex cohort, MajesTEC-1 patients were on average younger, they had a longer time since diagnosis, had a higher number of prior LOTs, were more refractory and more likely to have received ASCT. SMDs in unadjusted comparisons were large (i.e., >0.2) for all variables, suggesting heterogeneity and that comparability between the two populations could be improved.

Table 25. SMD for unadjusted and adjusted differences between MajesTEC-1 and the PomDex ECOG 0/1 cohort (adjustment for six variables)

	Before adjustment			After adjustment (n=6)		
	Teclistamab	PomDex	SMD	Teclistamab	PomDex	SMD
N	165	645	-	165	645	-
Refractory status, n (%)						
≤ double refractory	37 (22.4)	325 (50.4)	[redacted]	[redacted]	325 (50.4%)	[redacted]
Triple/quad refractory	78 (47.3)	291 (45.1)		[redacted]	291 (45.1%)	
≥ penta refractory	50 (30.3)	29 (4.5)		[redacted]	29 (4.5%)	
Number of prior LOTs, n (%)						
≤4	78 (47.3)	534 (82.8)	[redacted]	[redacted]	534 (82.8%)	[redacted]
≥5	87 (52.7)	111 (17.2)		[redacted]	111 (17.2%)	
ECOG performance status, n (%)						
0	55 (33.3)	133 (20.6)	[redacted]	[redacted]	133 (20.6%)	[redacted]
1	110 (66.7)	512 (79.4)		[redacted]	512 (79.4%)	
Age, n (%)						
<65	86 (52.1)	154 (23.9)	[redacted]	[redacted]	154 (23.9%)	[redacted]
≥65	79 (47.9)	491 (76.1)		[redacted]	491 (76.1%)	
Prior autologous stem cell transplantation, n (%)						
Yes	135 (81.8)	225 (34.9)	[redacted]	[redacted]	225 (34.9%)	[redacted]
No	30 (18.2)	420 (65.1)		[redacted]	420 (65.1%)	
Time (months) since diagnosis, n (%)						
1–47	43 (26.1)	268 (41.6)	[redacted]	[redacted]	268 (41.6%)	[redacted]
48+	122 (73.9)	377 (58.4)		[redacted]	377 (58.4%)	

Abbreviations: ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; LOT: line of treatment; PomDex: pomalidomide in combination with dexamethasone; sATC: stabilised average treatment effect for the control; SMD: standardised mean difference.

Figure 26: SMDs between the MajesTEC-1 and PomDex cohorts, before and after adjustment for six variables

Footnotes: red triangle (unadjusted means), blue circle (sATC).
Abbreviations: ECOG: Eastern Cooperative Oncology Group; PomDex: pomalidomide in combination with dexamethasone; SMD: standardised mean difference.

Figure 27: Distribution of PSs before weighting for patients in MajesTEC-1 and the PomDex cohort (ECOG Performance Status 0/1 subset)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PomDex: pomalidomide in combination with dexamethasone; PS: propensity score.

After adjustment (6-variable adjustment)

As noted previously, the ATC weighting approach was preferred in the current analysis. Additional adjustment was done to return to original sample sizes (for details, see Appendix D), which was referred to as 'scaled weights for average treatment effect for the control' (sATC).

Following the adjustment for the six variables, three out of the six variables had SMDs above the threshold of 0.2, indicating differences in baseline characteristics between studies persisted post-

adjustment (see Table 25). These disparities between the populations are also evident in the histograms of the PSs, as shown in Figure 28.

Figure 28: Distribution of PSs after sATC weighting for patients in MajesTEC-1 and the PomDex cohort (ECOG Performance Status 0/1 subset, adjusted for six variables)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PomDex: pomalidomide in combination with dexamethasone; PS: propensity score.

After adjustment (5-variable adjustment)

Removal of ASCT as an adjustment factor

As the 6-variable adjustment did not sufficiently adjust for differences in baseline characteristics between the two studies, it was necessary to consider an alternative set of adjustment factors. Clinical experts in RRMM were consulted for input on the importance of the six variables as prognostic factors in TCE RRMM. All four clinicians identified ASCT as one of the lowest priority prognostic variables, highlighting that it is not a significant prognostic factor in the RRMM patients who have received three prior therapies.[83] Additionally, clinicians indicated that age is highly correlated with prior ASCT, meaning adjustment for age enables adjustment for prior ASCT.

To assess the suitability of removing prior ASCT as an adjustment factor from the primary analysis, the prognostic impact for OS and TTNT was assessed. Table 26 presents HRs for OS and TTNT for patients who have had a prior transplant, compared to those who have not had a prior transplant. There was no statistically significant difference in clinical outcomes (OS, TTNT) of patients with or without prior ASCT. This was observed in both MajesTEC-1 and in the PomDex cohort of the UK RW TCE cohort study. Together, these data demonstrate that prior ASCT is not a prognostic factor for OS or TTNT thereby supporting the appropriateness of removing ASCT as an adjustment variable from the primary analysis.

Table 26. Prognostic impact of prior transplant in MajesTEC-1 and PomDex

Study	OS HR (95% CI)	p-value	TTNT HR (95% CI)	p-value

MajesTEC-1 No prior transplant (n=30) Prior transplant (n=135)				
PomDex No prior transplant (n=420) Prior transplant (n=225)				

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PomDex: pomalidomide in combination with dexamethasone; TTNT: time to next treatment.

Therefore, prior ASCT was removed from the weighting process and the populations were re-adjusted using five adjustment factors (see Table 27, Figure 26 for SMDs after adjustment). The removal of ASCT from the adjustment process resulted in significant improvements in overlap between the two populations, as represented by Figure 29 and Figure 30.

Adjustment for five variables (refractory status, number of prior lines of therapy, months since diagnosis, age and ECOG score) was considered to represent the most appropriate approach for the primary ITC analysis, since the overlap between the populations improved notably versus the six-variable approach. It should be noted that adjusting for five variables also produced more conservative results for teclistamab compared to the ITC adjusting for six variables (Section B.2.9.5).

Table 27. SMD for unadjusted and adjusted differences between MajesTEC-1 and the PomDex ECOG 0/1 cohort (adjustment for five variables)

	Before adjustment			After adjustment (n=5)		
	Teclistamab	PomDex	SMD	Teclistamab	PomDex	SMD
N	165	645	-	165	645	-
Refractory status, n (%)						
≤ double refractory	37 (22.4)	325 (50.4)	[redacted]	[redacted]	325 (50.4%)	[redacted]
Triple/quad refractory	78 (47.3)	291 (45.1)		[redacted]	291 (45.1%)	
≥ penta refractory	50 (30.3)	29 (4.5)		[redacted]	29 (4.5%)	
Number of prior LOTs, n (%)						
≤4	78 (47.3)	534 (82.8)	[redacted]	[redacted]	534 (82.8%)	[redacted]
≥5	87 (52.7)	111 (17.2)		[redacted]	111 (17.2%)	
ECOG performance status, n (%)						
0	55 (33.3)	133 (20.6)	[redacted]	[redacted]	133 (20.6%)	[redacted]
1	110 (66.7)	512 (79.4)		[redacted]	512 (79.4%)	
Age, n (%)						
<65	86 (52.1)	154 (23.9)	[redacted]	[redacted]	154 (23.9%)	[redacted]
≥65	79 (47.9)	491 (76.1)		[redacted]	491 (76.1%)	
Prior autologous stem cell transplantation, n (%)						
Yes	135 (81.8)	225 (34.9)	[redacted]	[redacted]	225 (34.9%)	[redacted]
No	30 (18.2)	420 (65.1)		[redacted]	420 (65.1%)	
Time (months) since diagnosis, n (%)						
1–47	43 (26.1)	268 (41.6)	[redacted]	[redacted]	268 (41.6%)	[redacted]
48+	122 (73.9)	377 (58.4)		[redacted]	377 (58.4%)	

Abbreviations: ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; LOT: line of treatment; PomDex: pomalidomide in combination with dexamethasone; sATC: stabilised average treatment effect for the control; SMD: standardised mean difference.

Figure 29: SMDs between the MajesTEC-1 and PomDex cohorts, after adjustment for five variables

Footnotes: red triangle (unadjusted means), blue circle (sATC).
Abbreviations: ECOG: Eastern Cooperative Oncology Group; PomDex: pomalidomide in combination with dexamethasone; SMD: standardised mean difference.

Figure 30: Distribution of PSs after sATC weighting for patients in MajesTEC-1 and the PomDex cohort (ECOG Performance Status 0/1 subset, adjusted for five variables)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PomDex: pomalidomide in combination with dexamethasone; PS: propensity score.

B.2.9.4 Results

The sATC-reweighted KM curve for teclistamab alongside the KM curve for PomDex are presented in Figure 31 and Figure 32 for OS and TTNT, respectively. The curves appear to run closely together for the first 3 months approximately, after which there is a clear separation. From this point, the adjusted curves for teclistamab illustrate the clear OS and TTNT benefits compared to PomDex, which extend until the end of follow-up.

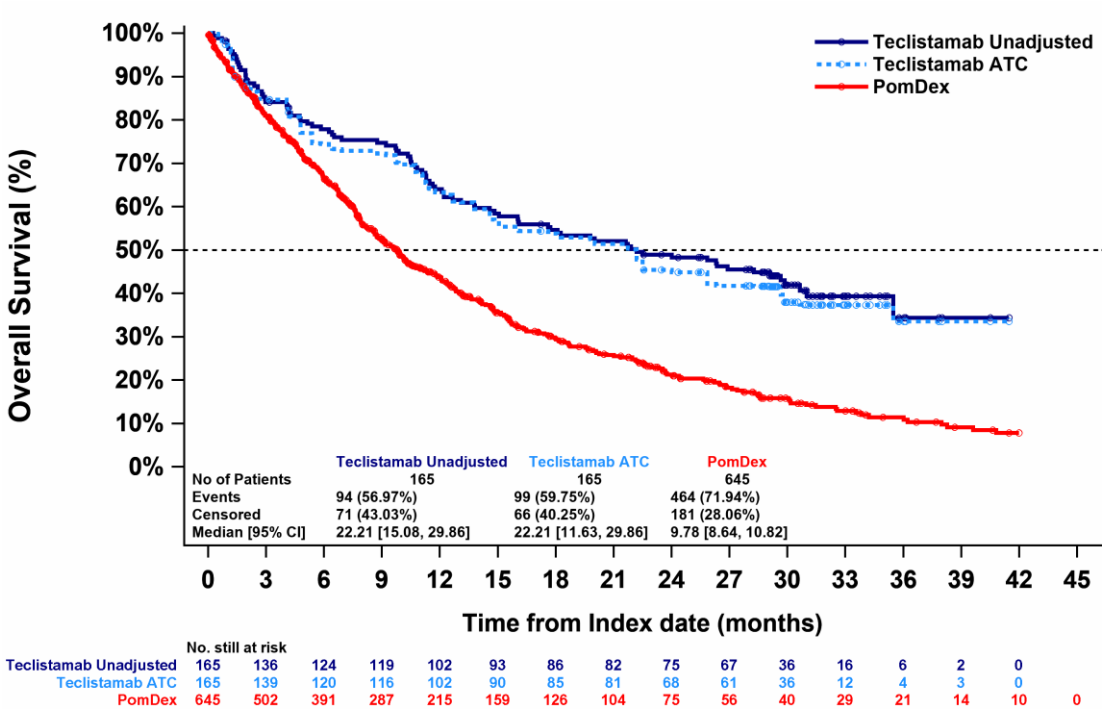
Treatment with PomDex is associated with a median TTNT and OS of just 7.03 and 9.78 months, respectively, emphasising the poor treatment outcomes in TCE RRMM patients who receive this treatment regimen after three prior therapies that included PI, IMiD and anti-CD38 mAb. In comparison, treatment with teclistamab is associated with a median TTNT and OS of 12.39 and 22.21 months, respectively (post- sATC weighting). Teclistamab therefore improves median TTNT by 5.36 months when compared to treatment with PomDex, representing a 76.2% increase. Teclistamab then provides patients with more than an additional year of life when compared to PomDex, extending median OS by 12.43 months, representing a 127.1% increase in OS with teclistamab treatment.

The estimates of the TTNT and OS treatment effect for teclistamab relative to PomDex after adjustment are presented in Table 28. The results demonstrate that teclistamab results in clinically meaningful and statistically significant improvements in OS and TTNT compared to PomDex. The base case sATC OS HR of 0.52 (95% CI: 0.36, 0.74) and TTNT HR of 0.56 (0.40, 0.79) indicate that teclistamab reduces the hazard of death by 48% and the hazard of disease progression by 44% when compared to PomDex.

The base case results were found to be robust, despite unavoidable uncertainty regarding both the weighting method and the number of variables adjusted for. The results across alternative estimands indicate that using alternative weighting approaches would be more favourable to teclistamab, suggesting that the base case approach is conservative. This is supported further by the results of additional sensitivity analyses presented in detail Section B.2.9.5, all of which were favourable for teclistamab when compared to the base case sATC IPTW approach. Moreover, the results of the naïve comparison are slightly more favourable towards teclistamab, as demonstrated by lower HRs for both OS and TTNT (Table 28), but are generally consistent with the base case ITC results. The consistency of the results across the base case and sensitivity analyses demonstrate the robustness of the results, and provide strong evidence to support the clinical benefits of teclistamab versus PomDex in the UK population.

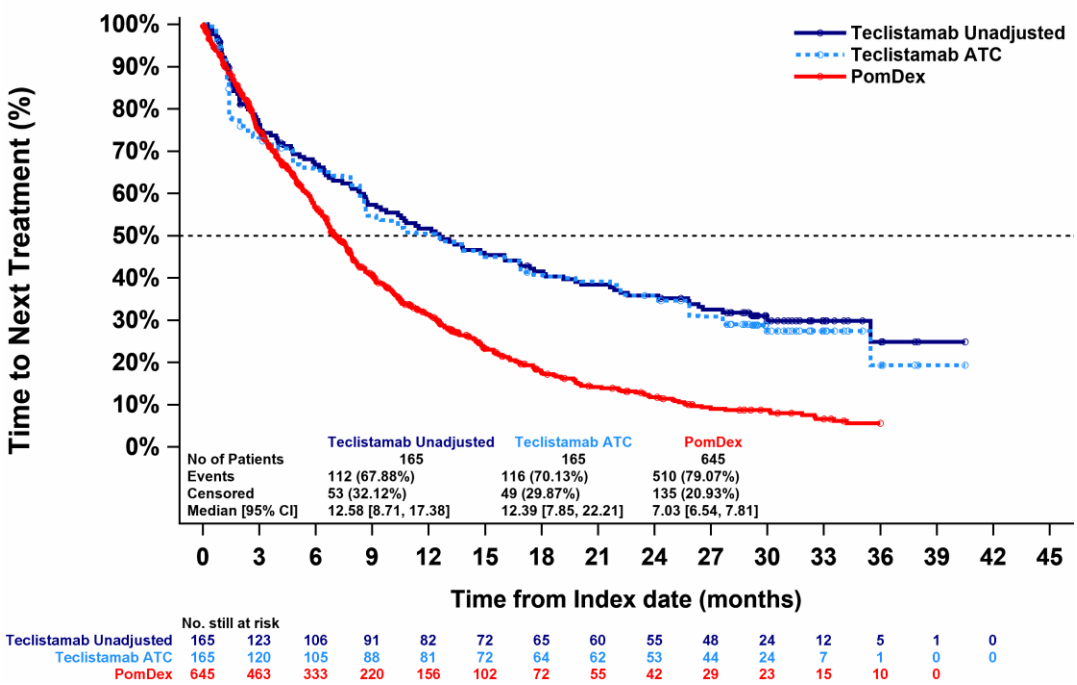
Overall, these findings highlight that teclistamab delivers a statistically significant and clinically meaningful extension of OS and TTNT when compared to the outcomes of TCE RRMM patients receiving PomDex in UK clinical practice. The results demonstrate the substantial clinical benefit associated with teclistamab consequent of its innovative mechanism of action. This is particularly of significance for a patient population who otherwise receives re-cycled treatments from previously trialled drug classes and consequently face a stark prognosis.

Figure 31: OS KM curves for teclistamab (before and after sATC weighting, adjustment for five variables) and PomDex



Abbreviations: KM: Kaplan-Meier; OS: overall survival; PomDex: pomalidomide in combination with dexamethasone.

Figure 32. TTNT KM curves for teclistamab (before and after sATC weighting, adjustment for five variables) and PomDex



Abbreviations: KM: Kaplan-Meier; PomDex: pomalidomide in combination with dexamethasone; TTNT: time to next treatment.

Table 28: Results of the ITC (ECOG Performance Status 0/1 subset, adjustment for five variables)

Comparison	OS HR (95% CI)	p-value	TTNT HR (95% CI)	p-value
Naïve	[redacted]	[redacted]	[redacted]	[redacted]
Weighting				
sATC (base case)	0.52 (0.36, 0.74)	<0.0001	0.56 (0.40, 0.79)	<0.0001

Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATT: average treatment effect on the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; TTNT: time to next treatment.

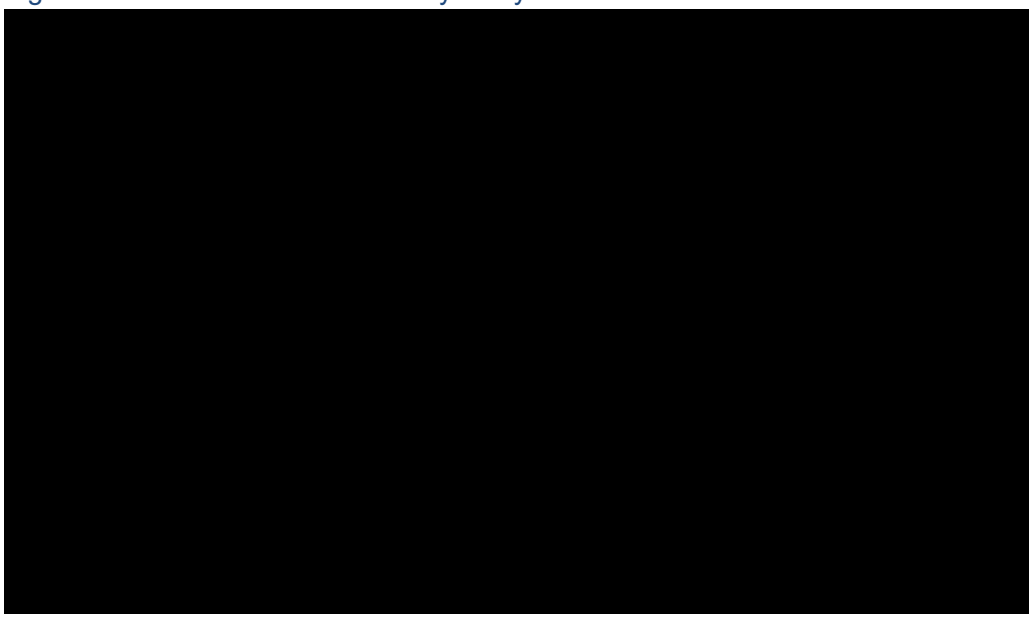
B.2.9.5 Sensitivity results

The results of twelve sensitivity analyses are presented for OS and TTNT in

Figure 33 and Figure 34, respectively, that explore a range of alternative ITC methodologies using both five adjustment variables in line with the base case approach, as well as six adjustment variables (5-variables plus prior ASCT).

The results of the sensitivity analyses show the base case approach is conservative. All other plausible ITC methodologies result in OS and TTNT HRs that are more favourable towards teclistamab, compared with the base case ATC analysis. The results show statistically significant differences for teclistamab across all of the analyses considered, with the majority of OS and TTNT HRs [redacted], strongly supporting the substantial clinical benefits that teclistamab provides over PomDex.

Figure 33: Base case and sensitivity analysis for OS



Footnotes: The 'ATC doubly robust' analysis adjusted for 5 variables, and added prior transplant as a covariate in the model.
Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATT: average treatment effect on the treated population; CI: confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting; ITC: indirect treatment comparison; OS: overall survival; TTNT: time to next treatment.

Figure 34: Base case and sensitivity analyses for TTNT

Footnotes: The 'ATC doubly robust' analysis adjusted for 5 variables, and added prior transplant as a covariate in the model.
Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATT: average treatment effect on the treated population; CI: confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting; ITC: indirect treatment comparison; OS: overall survival; TTNT: time to next treatment.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

The above analysis showed that adjusting the five variables improved comparability of the MajesTEC-1 population and the PomDex cohort in the UK RW TCE cohort study. The MajesTEC-1 population was adjusted to the PomDex cohort, as the UK RW TCE database provides evidence for the target patient population of relevance who would receive teclistamab in UK clinical practice i.e., patients with TCE RRMM receiving PomDex after at least three prior therapies. As such, all efforts have been made to ensure that the results of the ITC can be considered as relevant to the population of interest for this submission. The availability of individual patient data from the UK RW TCE cohort study enabled the use of propensity-based ITC methodologies, which allows for a more robust matching process compared to MAICs, which only match to aggregate reported baseline characteristics. After adjustment for five variables in the base case analysis, the MajesTEC-1 population was closely aligned to the UK RW TCE cohort study population based upon observable characteristics, with all SMDs <0.2.

Weighting variables

Nevertheless, the ITC was limited by the presence of potentially important differences that could not be adjusted for. This represents an unavoidable limitation of the available evidence base, due to the lack of data from the UK RW TCE cohort study relating to potentially important prognostic factors and treatment effect modifiers, as these data are not routinely collected in UK clinical practice.[145] Janssen acknowledges the potential for residual confounding; however, there is no *a priori* reason to expect that this bias would act in favour of teclistamab.

TTNT as a proxy for PFS

In the absence of data from the UK RW TCE cohort study sufficient for defining disease progression according to IMWG criteria, TTNT was used as a proxy for PFS from both the UK RW TCE cohort study and MajesTEC-1. TTNT was considered to represent a suitable proxy for PFS by clinical experts consulted during interviews conducted by Janssen throughout December 2023, and was considered acceptable by the EAG clinical advisors assessing the cilta-cel submission (TA889).[83] Furthermore, the overlap between TTNT and PFS is demonstrated by data from MajesTEC-1 (Section B.2.6.6; Figure 16). Clinical experts noted that TTNT was an appropriate proxy to use for PFS given overlap in results and the lack of PFS data from the UK RW TCE cohort study.[83] Whilst the use of TTNT represents a potential limitation, there is unlikely to be significant bias in the PFS estimate inferred from TTNT at this stage in therapy. Additionally, since TTNT was used as a proxy for teclistamab and PomDex, it is unlikely to impact the overall results of the ITC analysis.

COVID-19

As discussed in Section B.2.6.7, it is important to note that in MajesTEC-1, 18/94 of the patient deaths were due to COVID-19 and it is highly likely that the observed OS data from MajesTEC-1 may underestimate the true survival that would be observed in UK clinical practice. Consequently, the results of the ITC analysis are likely to be conservative and the benefits of teclistamab compared to PomDex may be even greater in clinical practice.

B.2.9.7 Conclusions of the indirect and mixed treatment comparisons

The UK RW TCE cohort study was considered to present the most appropriate source of evidence for the comparator, PomDex. The study was designed and conducted based on the principles outlined in the NICE RWE framework and further methodological details can be found in the DataSAT tool and risk of bias assessments presented in Appendix D.

Using the best evidence available, the ITC demonstrates that teclistamab consistently results in statistically significant improvements in OS and PFS [using TTNT as a proxy], versus PomDex in the UK RW TCE cohort study. These differences are clinically meaningful, resulting in an OS HR of 0.52 (0.36, 0.74; p<0.0001) and PFS HR of 0.56 (0.40, 0.79; p<0.0001) for teclistamab versus PomDex. These HRs translate to reductions in the risk of death by 48% and risk of progression or death by 44%, and extensions of median OS of 12.43 months (representing a 127.1% increase) and median PFS of 5.36 months (representing a 76.2% increase). Together, these findings represent marked improvements in the length of time that patients remain progression-free and alive, in a setting where they would otherwise face extremely poor prognoses when receiving PomDex. It should additionally be highlighted that a substantial proportion of patients in MajesTEC-1 were still experiencing ongoing CRs or better at the time of the latest DCO, and the potential for these patients to survive for extended periods of time is not captured in the observed data in MajesTEC-1. As such, these results likely represent a conservative estimate of the true magnitude of benefit of teclistamab.

The clinical benefit of teclistamab over PomDex was consistently observed across a broad range of sensitivity analyses that explored the impact of alternative ITC methodologies, estimands and weighting variables. The base case analysis produced the most conservative results of all sensitivity analyses, including the naïve (unadjusted) comparison, which provides strong

evidence for the statistically significant and clinically meaningful benefits of teclistamab versus PomDex.

B.2.10 *Adverse reactions*

B.2.10.1 Treatment duration and dosage

A summary of treatment duration and dose intensity of patients receiving teclistamab in MajesTEC-1 is provided in Table 29. The median duration of study treatment for patients in the All Treated Analysis Set was [redacted] months ([redacted] to [redacted] months), with a median dose intensity across all treatment cycles of [redacted] ug/kg/week ([redacted] to [redacted] ug/kg/week).

In MajesTEC-1, patients were permitted to switch to a reduced dosing frequency of teclistamab upon meeting the criteria outlined in Table 6. In total, 65 patients (39.3%) in the All Treated Analysis set switched from weekly to Q2W dosing. At the latest DCO (August 2023), 38 patients remained on treatment with teclistamab, with only [redacted] patient still on QW dosing.[105]

Table 29: Summary of the treatment duration and dose intensity in patients receiving teclistamab; All Treated Analysis Set

	All Treated Analysis Set N=165
Duration of study drug (months)	
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Dose intensity (All treatment cycles, ug/kg/week)[a]	
Mean (SD)	[redacted]
Median	[redacted]
Range	[redacted]
Number of doses	
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 teclistamab after step-up dosing period.
Abbreviations: RP2D: recommended Phase II dose; SD: standard deviation.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.10.2 Summary of treatment-emergent adverse events

A summary of the treatment-emergent adverse events (TEAEs) in the All Treated Analysis Set is provided in Table 30. At least one TEAE was experienced by [redacted] patients in the trial. [redacted] patients ([redacted]%) had reported at least one TEAE of any grade, including [redacted] patients ([redacted]%) with at least one TEAE that was judged as being due to teclistamab. Serious TEAE(s) were reported in [redacted]% of patients. Maximum Grade 3 TEAE(s) were reported for [redacted]% and maximum Grade 4 TEAE(s) were reported for [redacted]% of patients. Additionally, [redacted]% of patients experienced a Grade

5 TEAE; [redacted] of these patients having a cause of death reported as AE (including 18 patients with maximum Grade 5 AE of COVID-19) and [redacted] having a cause of death reported as progressive disease. [redacted] of the Grade 5 TEAEs were judged by the investigator to be related to teclistamab.[105] The rates of TEAEs leading to discontinuation were low in the All Treated Analysis Set, with 8 patients (4.8%) discontinuing due to a TEAE.[105]

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).[106] 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.[106] 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.[100]

Beyond COVID-19, the clinicians also noted that the safety profile for teclistamab has improved versus the results observed in MajesTEC-1, as they are now more experienced with using teclistamab and managing the associated side effects.[83]

Table 30: Summary of treatment-emergent adverse events; All Treated Analysis Set

TEAEs, n (%)	All Treated Analysis Set N=165
TEAE leading to discontinuation of study drug[a]	**8 (4.8%)**
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]
Death due to COVID-19	18 (10.9%)
COVID-19 TEAEs	[redacted]
COVID-19 serious TEAEs	[redacted]

[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: CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; RP2D: recommended Phase II dose; TEAE: treatment-emergent adverse event.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.10.3 Most common treatment-emergent adverse events

A summary of the most common TEAEs of any grade occurring in ≥20% of patients and the most common Grade 3 or 4 TEAEs occurring in ≥5% of patients for the All Treated Analysis set is presented in Table 31. The most common TEAEs of any grade were CRS, neutropenia and anaemia, occurring in 72.1%, 71.5% and 55.2% of patients, respectively. The most common Grade 3 or 4 TEAEs were neutropenia, anaemia and lymphopenia, occurring in 65.5%, 37.6% and 34.5% of patients, respectively.

A reduction in new onset Grade 3 or above infections was also observed in patients who switched to Q2W dosing in the All Treated Analysis set, as demonstrated in Figure 35. By one year, patients who switched to Q2W dosing had fewer Grade 3 or above treatment-emergent infections between 1 and 1.5 years than those who remained on QW dosing by 1 year ([redacted]% versus [redacted]%).

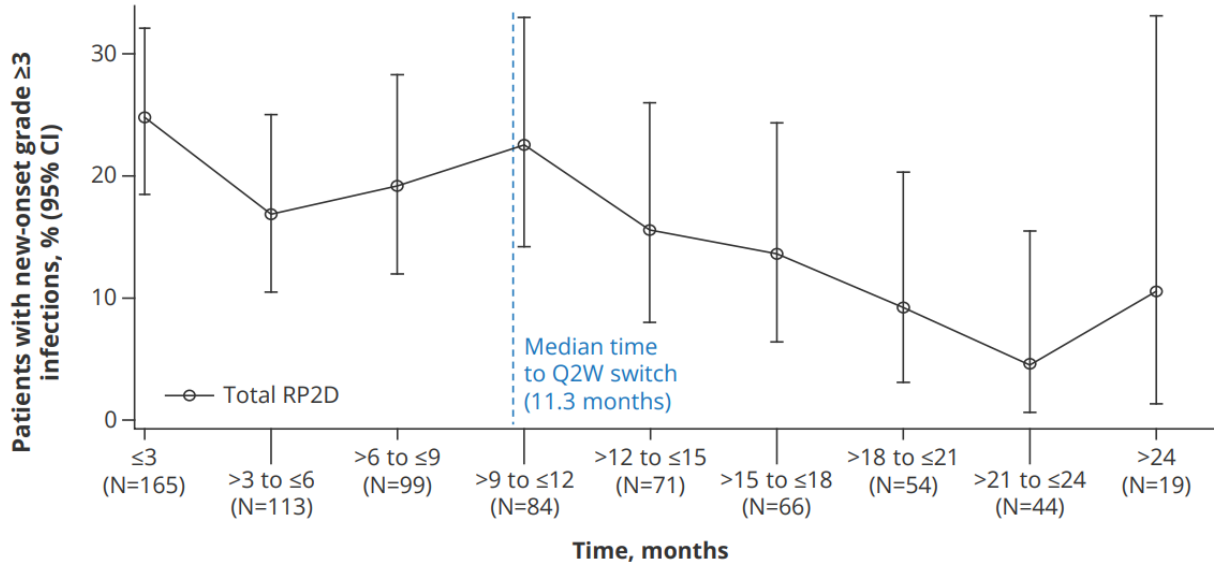
Table 31. Summary of most common (≥20%) TEAEs of any grade and most common (≥5%) Grade 3 or 4 TEAEs by system, organ, class

TEAEs, n (%)	All Treated Analysis Set N=165	
	Any Grade	Grade 3 or 4
Blood and Lymphatic System Disorders		
Neutropenia	118 (71.5%)	108 (65.5%)
Leukopenia	33 (20.0%)	15 (9.1%)
Anaemia	91 (55.2%)	62 (37.6%)
Thrombocytopenia	69 (41.8%)	38 (23.0%)
Lymphopenia	60 (36.4%)	57 (34.5%)
General Disorders and Administration Site Conditions		
Fatigue	[redacted]	[redacted]
Pyrexia	51 (30.9%)	1 (0.6%)
Injection site erythema	44 (26.7%)	0 (0.0%)
Immune System Disorders		
CRS	119 (72.1%)	1 (0.6%)
Pneumonia	[redacted]	[redacted]
COVID-19	48 (29.1%)	35 (21.2%)
Gastrointestinal Disorders		
Diarrhoea	57 (34.5%)	6 (3.6%)
Nausea	45 (27.3%)	1 (0.6%)
Constipation	37 (22.4%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	42 (25.5%)	2 (1.2%)
Metabolism and Nutrition Disorders		
Hypophosphatemia	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders		

TEAEs, n (%)	All Treated Analysis Set N=165	
	Any Grade	Grade 3 or 4
Cough	46 (27.9%)	0 (0.0%)
Nervous System Disorders		
Headache	40 (24.2%)	1 (0.6%)
Vascular Disorders		
Hypertension	[redacted]	[redacted]

Abbreviations: TEAE: treatment-emergent adverse event.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

Figure 35: Change in infection rate over time in patients who switched to Q2W dosing



Abbreviations: CI: confidence interval; Q2W: once every other week.
Source: Usmani *et al.* (2023).[110]

B.2.10.4 Adverse events of special interest – CRS

A summary of the treatment-emergent CRS events in the All Treated Analysis set is presented in Table 32. As of the latest DCO (August 2023), at least one event of any grade CRS was reported for 119 patients (72.1%), including [redacted] patients ([redacted]%) with at least one event of any grade CRS from the primary DCO analysis (September 2021). Almost all CRS events had a maximum severity of Grade 1 ([redacted] patients) or Grade 2 ([redacted] patients). Only one patient (0.6%) experienced a maximum of Grade 3 CRS, which was concurrent with serious Grade 3 pneumonia, and no events of Grade 4 or 5 CRS were reported.

UK clinical experts were consulted to understand how CRS events would be managed in UK clinical practice – further details are provided in Section B.3.5.3.

Table 32. Summary of treatment-emergent CRS events

CRS event/category, n (%)	All Treated Analysis Set (N=165)
Number of patients with CRS	119 (72.1%)
Number of patients with multiple CRS events	[redacted]
Median time to onset relative to most recent dose (range), days	[redacted]
Duration of CRS, median (range), days	[redacted]
Number of patients with CRS leading to discontinuation of teclistamab	[redacted]
Maximum toxicity grade	
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	1 (0.6%)
Grade 4	0
Grade 5	0
Patients with supportive measures to treat CRS	
Tocilizumab	[redacted]
Multiple doses at any time during study	[redacted]
>1 dose for a single CRS event	[redacted]
Corticosteroids	[redacted]
IV fluids	[redacted]
Single vasopressor	[redacted]
Low-flow oxygen by nasal cannula	[redacted]
Other	[redacted]
Outcome of CRS[a]	
CRS events with an outcome of recovered or resolved	[redacted]

[a] Patients may appear in more than one category. Occurrence is based on the last treatment visit on or prior to the day in which the TEAE occurred. [b] Prior to Cycle 1.
Abbreviations: CRS: cytokine release syndrome; IV: intravenous; SD: standard deviation.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO).[105]

B.2.11 *Ongoing studies*

B.2.12 [redacted]

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

Unmet need in the TCE RRMM population

Owing to the lack of novel and effective treatment options, patients in the UK with TCE RRMM currently face extremely poor clinical outcomes, with median TTNT and OS of just 7.03 and 9.78 months, respectively, when treated with PomDex. In addition to the poor prognosis, patients with TCE RRMM experience particularly poor HRQoL as a result of the increasing symptom burden with each successive LOT, coupled with high levels of emotional distress.[34, 102, 103] There is therefore a significant unmet need in TCE patients for an effective and well-tolerated treatment option with a novel mechanism of action that can potentially improve response depths and prolong PFS, resulting in improvements in patient HRQoL, and ultimately OS.

Principal findings of MajesTEC-1

The pivotal evidence for teclistamab in this submission is provided by MajesTEC-1, a three-part Phase I/II, open-label, single-arm study in patients with TCE RRMM.[105]

Multiple DCOs from MajesTEC-1 are available; regulatory approval for teclistamab was granted based on evidence from the March 2022 DCO (median follow-up of 14.1 months) whilst evidence in this submission is based on the [redacted] August 2023 DCO (median follow-up of 30.4 months).[105] ORR results were consistent over time across the DCOs of MajesTEC-1, with an initial ORR of 62.0% reported for the September 2021 DCO which increased to, and stabilised at, 63.0% for all subsequent DCOs (Table 13). Similarly, median OS demonstrated a gradual increasing trend over time with a median OS of 18.3 months (95% CI: 15.1, NE) reported in the March 2022 DCO, rising to 21.9 months (95% CI: 15.1, NE) and 22.2 months (95% CI: 15.1, 29.9) in the January 2023 and August 2023 DCOs, respectively, providing confidence in the long-term efficacy of teclistamab in this population.[105]

Response

The results of MajesTEC-1 demonstrate that treatment with teclistamab was associated with clinically meaningful rapid, deep and durable responses. The high ORR of 63.0% reported at the latest DCO included 46.1% of patients achieving a CR or better.[105] Almost all responders achieved a VGPR or better (98/104); the ≥VGPR rate in MajesTEC-1 was 59.4% (95% CI: [redacted], [redacted]).

Disease control was highlighted as the most important attribute for a treatment by patients in a 2019 Myeloma UK study. The high level of disease control achieved by patients in MajesTEC-1 therefore demonstrates the ability of teclistamab to fulfil this important outcome for patients.[157]

Recent RWE studies of patients receiving teclistamab have supported the results of the MajesTEC-1 trial, reporting ORRs to teclistamab of 59.3% (Reidhammer *et al.* [2024]) and 64% (Dima *et al.* [2023] in patients with TCE RRMM in clinical practice.[108, 127] Of the N=102 patients included in Dima *et al.* (2023), 80% would not have met the MajesTEC-1 eligibility criteria for reasons including an ECOG PS ≥2 (28%), Grade 3-4 anaemia (26%) and Grade 3-4 thrombocytopenia (20%), demonstrating the generalisability of the MajesTEC-1 results to patients in clinical practice.

These results further highlight the deep and durable responses associated with teclistamab.[140] Furthermore, an SLR conducted in 2022 to identify data on the relationship between HRQoL and clinical response concluded that deeper responses result in improved HRQoL in patients with MM.[84] It is therefore also anticipated that the depth of response would have a significant impact on how people perceive their future prospects, with patients achieving deeper responses anticipated to be more hopeful about their future prognosis.

Naïve Comparison Versus PomDex

Response rates in the population of patients with TCE RRMM are currently extremely poor. In the absence of response data reported in the UK RW TCE cohort study, ORR with PomDex was sourced from the MM-003 trial and ICARIA-MM trial (see Table 33 below). [85, 158] Notably, both trials are substantially less heavily pre-treated than the patient population of relevance to this submission – both trials only required patients to have received two prior therapies, and neither trial required patients to be TCE, with ICARIA-MM explicitly excluding patients who were refractory to anti-CD38 mAbs.[4, 85] These reported ORRs may therefore overestimate the benefits of PomDex in the TCE RRMM patient population of relevance to this submission.

Table 33 below shows that teclistamab consistently provides higher response rates when compared to PomDex.

Table 33: Comparison of ORR and ≥VGPR outcomes in patients receiving teclistamab, PomDex and teclistamab monotherapy

Outcome	MajesTEC-1 (teclistamab)	ICARIA-MM (PomDex)	MM-003 (PomDex)
ORR (%)	63.0	35.3	32.0
≥VGPR (%)	59.4	8.5 (VGPR)	7.0
≥CR (%)	46.1	1.3	NR

Abbreviations: CR: complete response; ORR: overall response rate; VGPR: very good partial response.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO);[105] Usmani *et al.* (2020);[159] Jesus *et al.* (2015);[85] Hulin *et al.* (2019).[158]

Survival outcomes

These rapid, deep and durable response rates translated to significant enhancements in survival outcomes with median PFS and OS results of 11.4 months (95% CI, 8.8 months to 16.4 months) and 22.2 months (95% CI, 15.1 to 29.9), respectively, observed in the MajesTEC-1 trial.[105] These overall survival outcomes do not capture the potential for long-term survival for those patients experiencing the deepest responses. Median OS, PFS and DOR amongst patients achieving a ≥CR in MajesTEC-1 were all found to be NE at the time of the latest DCO, highlighting the substantial improvement in all three outcomes in patients achieving >CR on teclistamab compared to PomDex.[105]

Additionally, the 25th percentile values for OS, PFS and DOR for patients who had achieved a CR or better were found to be [redacted] months, [redacted] months and [redacted] months, respectively. In comparison, 25th percentile values for OS, PFS and DOR in the overall All Treated Analysis Set was [redacted] months, [redacted] months and [redacted] months, respectively.[105] These data demonstrate the improved efficacy outcomes in patients achieving a deeper treatment responses, illustrating the

potential for long-term survival benefit for these patients. In particular, it is noted that as a substantial proportion of patients were still experiencing ongoing complete responses or better at the time of the latest DCO, the potential for these patients to survive for extended periods of time, and therefore the full extent of teclistamab efficacy, may not be fully captured in the MajesTEC-1 trial data presented in this submission. This was also demonstrated by the median OS not being reached for the population of patients in MajesTEC-1 who achieved a CR or better.

Together, the rapid, durable and deep response rates observed in MajesTEC-1 and the substantial and clinically meaningful improvement in PFS and OS highlight the benefit that teclistamab can bring to TCE RRMM patients in the UK. These benefits are consequential of the novel mechanism of action of teclistamab. In particular, teclistamab has demonstrated similar efficacy (whilst being an off-the-shelf treatment) to the licensed first-in-class BCMA CAR-T cell therapy idecabtagene vicleucel, which was reported to have a median OS and PFS of 19.4 months and 8.8 months, respectively.[119]

Safety profile

In addition to the step-change efficacy results, teclistamab was associated with a favourable safety profile with clinically manageable risks in patients with heavily pretreated RRMM, with AEs rarely leading to treatment discontinuation (only 4.8% of patients in the All Treated Analysis set experienced a TEAE leading to discontinuation of teclistamab). The most frequently reported TEAEs of any grade were CRS, neutropenia and anaemia, occurring in 72.1%, 71.5% and 55.2% of patients, respectively. However, these AEs can be effectively managed with available treatments and the step-up dosing schedule is used to mitigate the risk of severe CRS.[105] Of note, only one patient in MajesTEC-1 experienced a Grade 3 CRS event, and no patients experienced a CRS event of Grade 4 or 5.[105] The incidence of infection rate was also shown to decrease when patients switched to a more convenient Q2W dosing.[110] Furthermore, UK clinical experts highlighted that the safety results of MajesTEC-1 could be negatively impacted by the COVID-19 pandemic and therefore likely represent a conservative estimate of the tolerability profile of teclistamab. In general, clinicians noted that due to growing experience with use of teclistamab, the safety profile would likely be improved in UK clinical practice compared to the MajesTEC-1 .[83]

Health-related quality of life

Teclistamab was associated with [redacted] in HRQoL over time that are aligned to patient preferences. Teclistamab provided [redacted] from baseline in MM-related symptoms such as pain and fatigue, global health status, and functioning measured by EQ-5D-5L VAS, EORTC QLQ-C30 and PGIS scores.[105] Due to the lack of new treatments with novel mechanism of action for patients with TCE RRMM, patients often experience high anxiety as they know the primary treatment options have been exhausted, with one in five patients worrying about dying.[34] The introduction of teclistamab and its associated potential for long-term survival will therefore partially alleviate this burden by providing reassurance and hope to patients with TCE RRMM who have otherwise reached the end of the treatment pathway and face the dearth of effective treatment options.

Indirect treatment comparisons

MajesTEC-1 is a single-arm trial and therefore no comparative data exist between teclistamab and PomDex. Evidence for PomDex was derived from the UK RW TCE cohort study commissioned by Janssen, and included real-world anonymised data from 645 RRMM patients receiving PomDex after three prior therapies in the UK. The use of this registry study to provide comparative efficacy evidence for PomDex for patients with TCE RRMM was previously accepted in the cilta-cel appraisal and deemed generalisable to UK patients.[9] An IPTW ITC was then conducted to obtain relative estimates of efficacy for teclistamab versus PomDex in the population of interest.

Findings from the ITC demonstrated that treatment with teclistamab results in statistically significant improvements in OS and PFS, using TTNT as a proxy, versus PomDex. These differences are clinically meaningful, with teclistamab resulting in an OS HR of 0.52 (0.36, 0.74; p<0.0001) and PFS HR of 0.56 (0.40, 0.79; p<0.0001). These HRs translate to a 48% reduction in risk of death and a 44% reduction in the risk of progression. In absolute terms, these differences lead to an extension of median OS of 12.43 months (representing a 2.27 fold increase in OS) and an extension of median PFS of 5.36 months (representing a 1.75 fold increase in PFS). These findings are marked improvements in the length of time that patients remain progression-free and alive, in a setting where they would otherwise face an extremely poor prognosis when receiving PomDex, with median TTNT and OS of just 7.03 and 9.78 months, respectively. In particular, treatment with teclistamab almost doubles life expectancy compared to PomDex, meaning that teclistamab would have definitively met the ‘old’ End of life (EoL) criteria, which aimed to improve the quality of care for individuals and their families nearing the end of their life.

The clinical benefit of teclistamab over PomDex was consistent across a broad range of sensitivity analyses, accounting for different numbers of covariates and weighting methods, with the base case ITC producing the most conservative results across all of the analyses considered. All sensitivity analyses found teclistamab to be significantly more effective than PomDex for all outcomes providing confidence in the clinical superiority of teclistamab versus PomDex in this setting.

Strengths and limitations of the clinical evidence base

MajesTEC-1 was conducted in line with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Steps taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and where applicable direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions were provided for collection, handling, storage, and shipment of samples.[105]

Due to the single-arm design of the MajesTEC-1 trial, no comparative evidence was available. However, a thorough approach to the ITC was taken by Janssen, with the commissioning of the UK RW TCE cohort study in order to provide evidence of comparative effectiveness between teclistamab and the relevant comparator in this indication. The UK RW study was conducted in TCE RRMM patients receiving PomDex in UK clinical practice and consequently, aligns exactly with the population of patients anticipated to receive teclistamab in UK clinical practice. This

results in a high degree of confidence that the observed OS and TTNT outcomes for teclistamab are generalisable to UK clinical practice for patients with TCE RRMM.

Overall, UK clinical experts in RRMM noted that baseline demographic and disease characteristics of patients in MajesTEC-1 were broadly generalisable to the population of patients expected to receive teclistamab in UK clinical practice, albeit slight differences in the baseline demographic and disease characteristics. Patients in MajesTEC-1 are more heavily pretreated, which the UK clinical experts anticipated would result in conservative estimates of the true efficacy of teclistamab.[83] Additionally, in the ITC analysis, the MajesTEC-1 population was adjusted to align with the UK RW TCE cohort study using ATC methodology, which improved comparability of the study populations and ensured that the analysis was conducted for a population that is reflective of patients who would be eligible for teclistamab in UK clinical practice. The ITC demonstrated teclistamab to have substantial clinical benefits compared to PomDex, in the base case analysis and across all sensitivity analyses conducted, with these favourable results considered to be conservative given the likely underestimation of survival in MajesTEC-1, due to the notable proportion (18/94) of patient deaths resulting from COVID-19.

Summary

The introduction of teclistamab into the UK RRMM clinical pathway would meet the substantial unmet need for novel, effective and well-tolerated treatment options for patients with TCE RRMM, who face a dearth of therapies at this stage of the pathway. Teclistamab has an innovative mechanism of action, and if introduced into the treatment pathway, would bring a novel class of MM treatment in the UK – the first new class of treatment since the introduction of anti-CD38 mAbs over 5 years ago.[38] As the ITC approaches supported by sensitivity analyses have shown, teclistamab can substantially prolong PFS and OS versus PomDex , whilst improving symptom burden for patients, along with the observed HRQoL improvements arising from this decrease in symptom burden. Furthermore, the results of MajesTEC-1 have demonstrated that teclistamab has remarkable clinical benefit due to the rapid, deep and durable ORR, even in the heavily pre-treated, high-risk trial population. When applying the ORR results to the ESMO-MCBS:H form 3 for single-arm trials in orphan diseases, teclistamab scored a Grade 4, meaning that the medicine provides the highest magnitude of clinical benefit to the TCE RRMM patients.[107] This further highlights the substantial contribution teclistamab could offer patients and clinicians in the management of TCE RRMM in UK clinical practice.

Overall, the introduction of teclistamab to UK clinical practice would provide reassurance and hope of improved HRQoL and lengthened survival, in a patient population who has otherwise reached the end of the treatment pathway and faces an extremely poor prognosis. Due to teclistamab providing an extension to life of almost double that of current treatments, teclistamab would have definitively met the old EOL criteria, which aimed to improve the quality of care for individuals and their families nearing the end of their life. The addition of teclistamab to the treatment pathway would therefore represent a step-change in the management of TCE RRMM.

B.3 Cost effectiveness

Summary of Cost-Effectiveness Model

- A cost-utility model was developed to estimate the cost-effectiveness of teclistamab versus PomDex for the treatment of RRMM patients after at least three prior therapies from a UK's NHS and PSS perspective
- Similar to previous NICE evaluations of MM therapies, the model was a partitioned survival model consisting of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death
- The baseline characteristics of patients in the model were based on the All Treated Analysis set of the MajesTEC-1 trial, adjusted to align with the UK RW TCE cohort study population via IPTW (ATC-adjusted, as previously detailed in Section B.2.9)

Base Case Extrapolations: OS and PFS

- A visual assessment of log cumulative hazard plots confirmed that the PH assumptions between teclistamab and PomDex did not hold, thus independent extrapolations were fitted to survival data for each treatment arm. Six standard parametric distributions were fitted to KM data (Exponential, Weibull, log-logistic, log-normal, Gompertz and Generalised Gamma).
- For teclistamab, PFS [using TTNT as a proxy], OS and TTD KM data from MajesTEC-1 were used. For PomDex, PFS [using TTNT as a proxy] and OS KM data from the UK RWE TCE study were used; TTD for PomDex was derived based on the PomDex PFS extrapolation
- The choice of base case extrapolations were based upon statistical fit as well as long-term clinical plausibility, with the lognormal being selected in the base case for teclistamab OS and PFS. To remove the effects of subsequent therapies in MajesTEC-1 that are not routinely commissioned in the UK (see Section B.3.3), the OS KM data were adjusted via the two-stage approach
- Teclistamab lognormal extrapolations for both PFS and OS were further calibrated to align with the midpoints of the UK clinical expert predictions of survival (10% and 5% for OS and PFS respectively at 10 years, and 3% and 1% for OS and PFS respectively at 15 years) via attenuation of the survival data
- As the survival estimates provided from the standard extrapolations of the PFS and OS data for PomDex aligned with the long-term survival estimates provided by the clinical experts, the statistically best fitting Gompertz extrapolation was selected to model OS and PFS for PomDex. As a conservative simplifying assumption, the survival data for PomDex was not adjusted for subsequent treatments not reimbursed in UK clinical practice

Model Inputs

- AEs were modelled based on the MajesTEC-1 trial for teclistamab and the MM-003 trial for PomDex
- In the base case economic analysis, health state utility values (HSUVs) were modelled to be treatment-dependent. Treatment-dependent HSUVs were considered appropriate given the major difference in mechanisms of action between teclistamab and PomDex: multiple studies have shown that MM treatments which drive a deeper response are associated with improvements in patient HRQoL.[84]
- Health state utilities were derived from the MajesTEC-1 trial for teclistamab. PFS utilities were modelled using a time-independent utility approach, based on the observed improvement in

HRQoL over time in MajesTEC-1

- In the absence of utility data for PomDex in the UK RW TCE cohort study, HSUVs for PomDex in the base case analysis were informed by the accepted utilities in TA510[38]/TA783[8]. As these utility values were based on a less-heavily treatment exposed MM population than the population of relevance to this submission, the use of these utility values represents a conservative assumption
- Cost inputs used in the model (administration, drug acquisition, AEs, monitoring costs, concomitant medication and end-of-life cost) are aligned with the accepted inputs used in prior evaluations in MM[160-162]

Summary of cost-effectiveness results

- Based on a proportional QALY shortfall of [redacted], teclistamab is eligible for a 1.2x severity modifier versus PomDex, highlighting the poor prognosis faced by patients with TCE RRMM
- Overall, the base case with-PAS ICERs for all comparisons demonstrated teclistamab to be a cost-effective use of NHS resource at a WTP £30,000 per QALY
- Additionally, in all base case analyses, teclistamab was associated with positive incremental LYGs ([redacted]) and QALYs (ranging from [redacted]) versus PomDex. These results highlight the improvements in both quality and length of life that teclistamab may offer to patients who are 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 robust to an extensive number of sensitivity analyses
- The DSA results identified a small number of key influential parameters such as the mean body weight of patients, the final time-dependent utility value for the PFS state and the PD health state utility value for teclistamab. At PAS price, teclistamab is associated with a positive incremental net health benefit (INHB) versus PomDex, in all cases
- Scenario analyses conducted to address sources of uncertainty in the model demonstrated that, whilst there was variation in the INHB, cost-effectiveness conclusions remained unchanged with teclistamab remaining dominant versus PomDex (at list price) at a willingness-to-pay threshold of £30,000 per QALY
- Overall, these results demonstrate that teclistamab could address a significant unmet need for a novel, effective and well-tolerated treatment option which is able to induce profound and enduring responses, translating to an anticipated increase in OS of [redacted] life years versus PomDex, whilst representing a cost-effective use of NHS resources
- These economic results omit important benefits that cannot be captured in the QALY, including the value of hope and real option value, as well as the impact of COVID-19 excess mortality on the MajesTEC-1 trial, which all mean that the base case results are likely to represent a conservative estimate of the true cost-effectiveness of teclistamab to patients in UK clinical practice (see Section B.3.13).

B.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 G, H and I.

The economic SLR was originally conducted on 2nd July 2020 and updated multiple times, with the most recent update conducted on 31st October 2023.

In total, 198 publications reporting on 169 unique studies met the inclusion criteria of the economic SLR. Among the included studies, seven unique studies reported data on TCE RRMM patients who had previously been treated with a PI, an IMiD, and an anti-CD38 antibody: two were published cost-utility analyses (CUAs), one was a cost effectiveness analysis (CEA), and four were HTA submissions. These studies are detailed in Appendix G.

B.3.2 *Economic analysis*

No relevant economic evaluations comparing teclistamab to PomDex from a UK perspective were identified in the SLR. As such, a *de novo* CUA 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 teclistamab versus PomDex for treating relapsed or refractory multiple myeloma after 3 treatments. The analysis was conducted from the perspective of the NHS and Personal Social Services (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 both in terms of life years gained (LYG) and QALYs gained
- The primary outcome measure for the economic evaluation was the ICER (cost per QALY gained) for the comparison of teclistamab versus PomDex
- Clinical effectiveness for teclistamab and PomDex was measured through OS and PFS outcomes (see Section B.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 B.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.

B.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 and have demonstrated disease progression on their last therapy (Section B.1.1). This is in line with the decision problem for this submission, the licensed indication for teclistamab in the UK and the All-Treated Analysis Set population enrolled in the MajesTEC-1 trial.[105, 139]

The characteristics of patients entering the model were based on the baseline characteristics of patients in the All Treated Analysis set of the MajesTEC-1 trial, adjusted to align with the UK RW TCE cohort study population. This adjustment was carried out via the main analysis IPTW approach using ATC weights presented previously in Section B.2.9.

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

A summary of the patient baseline characteristics used in the economic model are presented in Table 34.

Table 34: Summary of baseline characteristics used in the economic model

Characteristics	TCE RRMM population	Source
Mean age, years	[redacted]	MajesTEC-1 (adjusted to align with the UK RW TCE cohort study population using IPTW with ATC weights)
Proportion of female patients, %	[redacted]	
Mean body weight, kg	[redacted]	
Mean BSA, m^2	[redacted]	

Abbreviations: ATC: average treatment effect for the control; BSA: body surface area; ECOG: Eastern Cooperative Oncology Group; NCRAS: National Cancer Registration and Analysis Service; IPTW: inverse probability of treatment weighting.

B.3.2.2 Model structure

The developed model consisted of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), 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 ATC weights as detailed in Section B.2.9 and adjusted for the impact of subsequent treatments on OS using the two-stage method as detailed in Section B.3.3.2) and the UK RW TCE cohort study for PomDex, which represent the main sources of clinical effectiveness evidence relevant to this submission. 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 36:

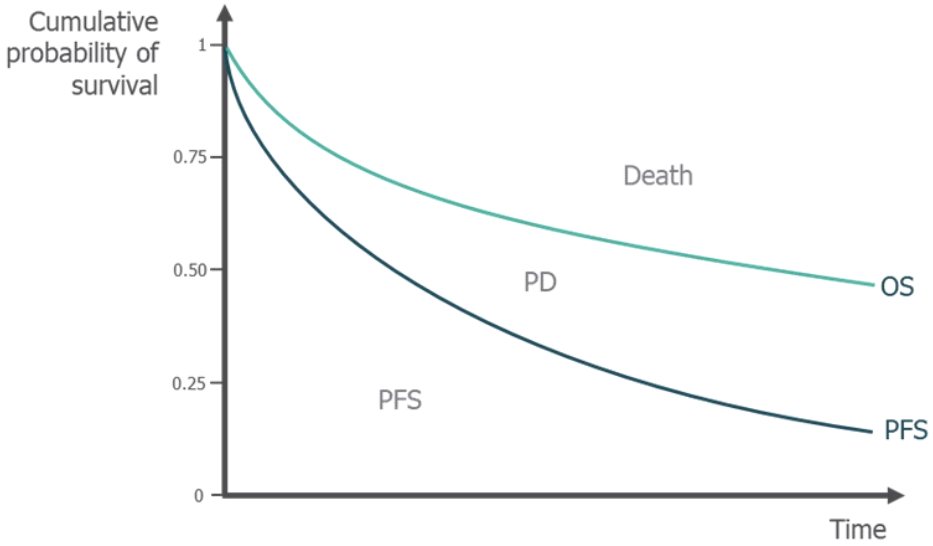
- The proportion of patients occupying the PF state was calculated as the proportion alive and progression-free (based on PFS extrapolations)
- The proportion of patients occupying the PD state was calculated as the proportion alive (based on OS extrapolations) minus the proportion of patients alive 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 teclistamab or PomDex for reasons other than disease progression. As such, time to treatment discontinuation (TTD) was used to determine the time on treatment (ToT) for patients who may have discontinued treatment before progression. This allowed for the application of specific health-state costs, such as treatment acquisition, treatment administration and monitoring costs, to be applied only while patients are on or off treatment, while also allowing patients to occupy the PF and PD health-states, regardless of whether they are on treatment.

The model used a cycle duration of one week in order to allow granular modelling of treatment costs; this is aligned with previous MM NICE submissions.[4, 8, 20, 22, 38, 100, 163, 164] A half cycle correction was applied in line with modelling best practice, to avoid systemic over or underestimation of costs and outcomes.[165]

Figure 36: Partitioned survival model structure



Abbreviations: OS: overall survival; PD: progressed diseased; PFS: progression-free survival.

Justification for choice of model structure

A partitioned survival model (PSM) was deemed the most appropriate model structure to inform the cost-effectiveness of teclistamab, as the modelled health states are considered to accurately reflect the natural disease course for patients with TCE RRMM. The key outcomes in this setting, PFS and OS, are time-to-event outcomes, and the PSM approach allows for the observed data from the MajesTEC-1 trial and the UK RW TCE cohort study to be directly and intuitively replicated within the economic model. This means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with teclistamab or PomDex.

In addition, the MajesTEC-1 trial has mature survival data after a median follow up of 30.4 months.[105] Mature survival data reduces uncertainty in the extrapolations, ensuring modelled events closely match observed data. The PSM structure allows uncertainty in long-term

extrapolations to be explored through scenario analyses utilising alternative survival distributions (see Section B.3.11.3).

Lastly, as MM is a chronic, incurable disease, there is no requirement for functionality to move backwards between the health states, thus further supporting the use of a PSM for the cost-effectiveness analysis. The choice of model structure is aligned with extensive precedent for the use and acceptance of PSMs in previous NICE appraisals.[4, 8, 20, 22, 38, 100, 163, 164].

The additional features of the economic analysis are outlined and justified in Table 35. No non-terminated previous NICE appraisals were identified for adult patients with TCE RRMM after three prior therapies, having demonstrated disease progression on the last treatment.

Table 35: Features of the economic analysis

Factor	Current evaluation	
	Chosen values	**Justification**
Model structure	Partitioned survival model	A partitioned survival model accurately reflects disease progression and the observed survival profile of patients with TCE RRMM treated with teclistamab or PomDex, and is in line with extensive precedent in previous NICE appraisals in RRMM.[166]
Time horizon	Lifetime	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
Cycle length	One week	A short cycle duration of one week allows granular modelling of treatment costs and is aligned with the weekly dosing regimen of teclistamab; the use of a one week cycle duration is aligned with previous NICE submissions in RRMM (TA338/427[163], TA510[38]/TA783[8] and TA505[164]/TA870[20], TA897[100] and ID2701[22])
Half cycle correction	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[165]
Source of utilities	• In the base case economic analysis, treatment-dependent health state utility values for the PF and PD health states were utilised • PF and PD health state utility values for teclistamab were derived from EQ-5D-5L data from the MajesTEC-1 trial, cross-walked to EQ-5D-3L based on Hernandez-Alava et al. (2017) dataset (Hernández Alava et al. 2020)[167-169] • In the PF health state for teclistamab, utilities were modelled to be time dependent • PF and PD health state utility values for PomDex were modelled to be time independent and were informed by the accepted values used in TA510[38]/TA783[8]	*Justification for treatment-dependent HSUVs* • As teclistamab is associated with deeper and more durable responses versus PomDex (>7-fold increase in the VGPR rate was achieved in patients receiving teclistamab versus PomDex), and multiple studies have shown that MM treatments which drive a deeper response are associated with improvements in patient HRQoL, therefore modelling of treatment-dependent HSUVs was considered appropriate • The MajesTEC-1 trial represents the only available source of utility data for teclistamab for patients with TCE RRMM after at least three prior therapies. As such, the health state utility values for teclistamab were informed by the MajesTEC-1 trial. *Justification for time-dependent HSUVs for the teclistamab arm* • The MajesTEC-1 trial demonstrated that patient utility values after being treated with teclistamab improved with increasing time spent in the PF

	• For both treatments, health state utility values 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[170] • Further details are provided in Section B.3.4.5	health state; the use of time-dependent utilities in the base case economic analysis was supported by feedback received from UK clinical experts in MM (Section B.3.4.5). *Justification for source of HSUVs for the PomDex arm* • In the absence of utility data for PomDex in patients with TCE RRMM, health state utility values for PomDex in the base case analysis were informed by the accepted health state utility values used for PomDex in TA510[38]/TA783[8], derived from the MM-003 trial. Given that TCE RRMM patients are likely to experience worsened HRQoL compared with the less heavily pre-treated patient population included in the MM-003 trial, the use of these utility values in the base case analysis represents a conservative assumption. • As there are no available data to suggest that utilities vary over time for patients treated with PomDex, the HSUV for PFS for PomDex was modelled to be time-independent in the base case analysis.
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 are based on established sources of costs within the NHS and are aligned with previous evaluations in MM[160-162]

Abbreviations: AE: adverse events; BMP: bortezomib, melphalan and prednisone; BNF: British National Formulary; CR: complete response; EQ-5D-5L: EuroQol-5D, 5 levels; eMIT: electronic market information tool; MRD; minimal residual disease; MM: multiple myeloma; NHS: National Health Service; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; RRMM: relapsed/refractory multiple myeloma.

B.3.2.3 Intervention technology and comparators

Teclistamab

The intervention included in the cost-effectiveness model was teclistamab. 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).[139] In line with data observed from the MajesTEC-1 trial ,the model assumed that a proportion of patients switch from QW to Q2W dosing (Section B.3.3.5).[27] The license states that teclistamab 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.

PomDex

As described in Section B.1.1, PomDex is considered to be the only relevant comparator to teclistamab in this submission. Patients are modelled to receive PomDex as per its marketing authorisation in 28-day treatment cycles, with patients receiving pomalidomide 4 mg orally once daily for the first 21 days of each 28-day treatment cycle and dexamethasone 40 mg orally once per day on Days 1, 8, 15 and 22 per each 28-day treatment cycle for at least 8 treatment cycles.[171]

B.3.3 *Clinical parameters and variables*

B.3.3.1 Survival inputs and assumptions

The economic model is a cohort-based PSM consisting of three mutually exclusive health states: PF, PD and death. The proportion of patients in each health state at each weekly model cycle was determined for teclistamab and PomDex from cumulative survival probabilities from PFS [using TTNT as a proxy], 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 and study follow-up data, the follow-up periods for MajesTEC-1 and the UK RW TCE cohort study were shorter than the model time horizon and extrapolations of the observed OS, PFS and TTD data were required.

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.[172] 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 the UK RWE TCE study, and clinical plausibility of long-term survival predictions.

The proportional hazard assumptions were tested via log cumulative hazard plots, Schoenfeld residual plots and Schoenfeld tests. The results of proportional hazards assessments and smoothed hazard plots for each of the endpoints can be found in Appendix N.

For OS, the teclistamab and PomDex curves in the log-cumulative hazard plots were not parallel, indicating that the PH assumption for OS was violated. Similar results were found in the Schoenfeld residual plot for OS for teclistamab and PomDex. Therefore, while the Schoenfeld p-value was >0.05, suggesting the PH assumption holds, given that both the log-cumulative hazard plot and Schoenfeld residual plot for OS suggest that the PH assumption is violated, it was considered more appropriate to independently extrapolate OS for teclistamab and PomDex in the base case economic analysis – particularly given the fundamental differences in mechanism of actions between the two treatments and the availability of patient level data from the MajesTEC-1 and UK RW TCE cohort study.

Similar evidence of violation of the proportional hazard assumption was found for TTNT [proxy for PFS], in particular, the p-value for the Schoenfeld residual plot was <0.05, providing further evidence that the PH assumption is violated for TTNT. As such, independent extrapolations for PFS for teclistamab and PomDex were also used in the base case economic analysis.

As such, in the base case analysis, independent models were fitted to the adjusted PFS [using TTNT as a proxy], OS KM (adjusted using IPTW based on ATC weights; Section B.2.9 and the two-stage method to account for subsequent treatments; Section B.3.3.2) and TTD KM data for MajesTEC-1, and PFS (using TTNT as a proxy) and OS KM data for the UK RW TCE cohort study. TTD for PomDex was derived based on the PomDex PFS extrapolation, as detailed in Section B.3.3.4.

The choice of distribution for the base case for each endpoint was informed considering:

- **Graphical assessment of fit**: visual inspection regarding how well the predicted extrapolation captured the shape of the observed Kaplan-Meier data
- **Statistical fit**: AIC and BIC statistics were generated for each extrapolation, the best fit to the observed data is the extrapolation with the lowest AIC and BIC
- **Clinical validation of long-term extrapolations for current treatments in clinical practice**: interviews with clinical experts were conducted, where clinicians were asked to provide lower plausible, most likely and upper plausible estimates of the proportion of patients in clinical practice expected to be progression-free and alive at 5-, 10- and 15-years following treatment with teclistamab or PomDex

B.3.3.2 Overall survival

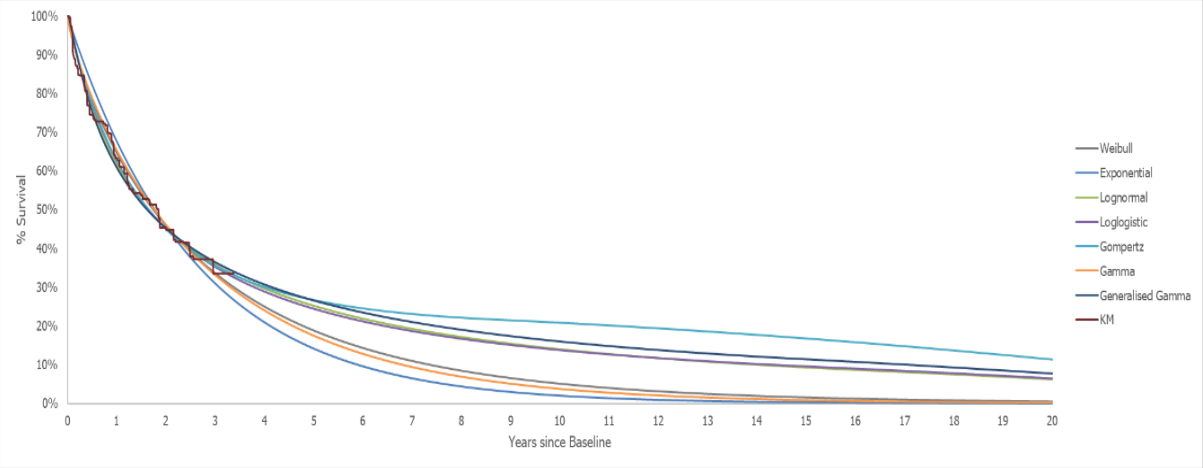
Teclistamab

Extrapolations were fitted to the OS data from MajesTEC-1 adjusted to match the UK RW TCE cohort study (Section B.2.9). Each of the OS extrapolations are presented in Figure 37 below, with goodness-of-fit statistics of each of the extrapolations presented in Table 36. Long-term estimates of OS for each parametric extrapolation are provided in Table 37, and the accompanying smoothed hazard plots for teclistamab OS are presented in Figure 38.

Mortality for patients with MM is expected to be higher than the mortality of the general population when matched for age and gender. To ensure that the hazard of death is at least equal to general-population mortality (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.

Figure 37: Extrapolation of OS for teclistamab using IPD from MajesTEC-1 (adjusted via IPTW using ATC weights to align with the UK RW TCE cohort study)



Note: Extrapolations shown are with the GPM cap applied
Abbreviations: GPM: general population mortality; IPD: individual patient data; NCRAS: National Cancer Registration Analysis Service; OS: overall survival; UK: United Kingdom.

Table 36: Goodness-of-fit statistics for teclistamab OS extrapolations

Survival model	Teclistamab			
	AIC	BIC	AIC Rank	BIC Rank
Lognormal	**1539.8**	**1546.1**	1	1
Generalised Gamma	1541.6	1551.0	2	5
Loglogistic	1543.2	1549.4	3	2
Gompertz	1543.7	1549.9	4	3
Weibull	1545.3	1551.6	5	6
Gamma	1546.3	1552.5	6	7
Exponential	1547.8	1550.9	7	4

Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; PomDex: pomalidomide and dexamethasone.

Table 37: Comparison of predicted survival rates for teclistamab OS extrapolations (with GPM cap)

Survival model	OS survival rates (%)			
	Teclistamab			
	Mean OS (months)	5 years	10 years	15 years
Clinical Expert Estimates				
Clinical expert estimates	NA	12–30%	5–15%	1–5%
Extrapolations				
Gompertz	69.1	26.72%	20.83%	16.78%

Generalised Gamma	59.1	26.63%	16.01%	11.40%
Lognormal	54.5	25.27%	14.00%	9.30%
Loglogistic	54.5	24.50%	13.78%	9.56%
Weibull	35.8	18.91%	5.12%	1.54%
Gamma	33.7	17.58%	3.77%	0.84%
Exponential	30.8	14.25%	2.02%	0.29%

Abbreviations: NA: not applicable; OS: overall survival; PomDex: pomalidomide and dexamethasone.

Figure 38. Hazard plot for OS, teclistamab, sATC(n =5)

Source: Janssen. Data on file. Analysis based on MajesTEC-1 Clinical Study Report (August 2023 DCO).
Abbreviations: DCO: data cut-off; OS: overall survival; sATC: scaled average treatment effect for the control.

Figure 38 shows that in MajesTEC-1, teclistamab is associated with an OS hazard rate which consistently decreases over time. The loglogistic, lognormal, Gompertz and Generalised Gamma extrapolations all broadly align with this trend. In contrast, the exponential (with a constant hazard of death), the Weibull and (non-generalised) Gamma extrapolations (with a hazard of death that remains relatively constant after 400 days) do not follow the observed hazards from MajesTEC-1 and lack internal validity.

Given the availability of extensive follow up from MajesTEC-1 (median follow up of 30.4 months), visual and statistical fit to the observed MajesTEC-1 data were also important determinants of the chosen base case extrapolation.[105] The lognormal extrapolation provided the best visual fit to the observed OS data from MajesTEC-1, as well as the best statistical fit to the observed OS data with respect to both AIC and BIC. With the exception of the Generalised Gamma, all of the

other extrapolations were at least 2 AIC points higher than the lognormal extrapolation, indicating that they provided a statistically significantly worse fit to the observed data in MajesTEC-1.[173, 174]

Based on internal validity, the lognormal extrapolation was therefore considered to represent the most appropriate base case extrapolation. In line with NICE TSD 14, it was then necessary to consider the external validity of the lognormal extrapolation, based on long-term predictions of survival provided by UK clinical experts.[83]

In considering the generalisability of the clinical data for teclistamab as well as the subsequent treatments available in UK practice compared to the MajesTEC-1 trial (further detailed in Section B.3.5.4), UK clinical experts estimated that long-term OS for teclistamab would range from 12–30% at 5 years, 5–15% at 10 years, and 1–5% at 15 years. They highlighted that these long-term survivors are likely to represent those patients who experienced the deepest responses to teclistamab – as previously detailed in Section B.2.6, 46.1% of patients experienced a ≥CR in MajesTEC-1, and among patients who experienced ≥CR in MajesTEC-1, the median DOR, PFS and OS were all NE at the time of the latest DCO, with a 24-month OS rate of [redacted]% (95% CI: [redacted], [redacted]%) for patients in CR or better.

However, compared to the expert predictions, the lognormal extrapolation appeared to slightly overestimate long-term OS for teclistamab, particularly at 15 years. The only extrapolation to fall within the clinical expert estimates of survival at both 10 and 15 years was the Weibull extrapolation. However, the Weibull extrapolation lacked internal validity, producing one of the worst statistical fits to the observed MajesTEC-1 data, while the plateauing hazard profile associated with the Weibull extrapolation did not match the consistently decreasing hazard of death observed in MajesTEC-1.

Considering the other extrapolations, all survival curves generated estimates within the clinical experts 5-year survival range. However, at 10 years, the exponential was too pessimistic and all other extrapolations were too optimistic versus the long-term estimates of survival except for the log-logistic, which fell within the range at 10 years but was too optimistic at 15 years, similar to the lognormal.

As such, considering both internal and external validity, none of the generated extrapolations appeared to be suitable for use in the base case economic analysis. Therefore, the extrapolation which provided the best statistical fit to the observed data from MajesTEC-1 and fell within the 5- and 10- year range provided by the clinicians (i.e., lognormal) was taken forward, and additional calibrations were explored in order to align the lognormal extrapolation with clinically plausible estimates of long-term survival for teclistamab.

OS adjustment to account for subsequent treatments not routinely available in the UK

To ensure that these extrapolations were indeed representative of what could be expected in UK clinical practice, subsequent treatment adjustment was also explored to account for the possible effects of subsequent treatments in the MajesTEC-1 trial not currently routinely available in UK clinical practice, which might have the potential to increase the predicted long-term estimates of survival (full details of subsequent treatments in MajesTEC-1 are presented in Section B.3.5.4).

Exploration of censoring and two-stage 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 N.1). As such, this censoring method was not considered further and an alternative method was explored whereby the OS KM data were adjusted using the simplified two-stage method outlined in NICE TSD 16.[175] NICE TSD 16 lists 3 advanced approaches to adjust for the impact of treatment switching on OS. The IPCW approach was explored, whereby in a first step patients receiving a subsequent treatment not routinely available in the UK were censored at time of initiation, and in a second step patients similar to the censored patients were upweighted.

This leads to counterfactual curves which were shifted upwards relative to the observed OS KM, which would suggest the treatments adjusted for were harmful for patients, which is clinically unplausible, and is rather indicating informative censoring which cannot be compensated by upweighting. The RPFST- method was considered not to be applicable, as it would require treatments to be adjusted for in both the teclistamab cohort as in the external UK RW TCE cohort. Therefore, an alternative method was explored whereby the OS KM data were adjusted using the simplified two-stage method outlined in NICE TSD 16. Using this method, the survival time was reduced for patients initiating a subsequent treatment which is not available in routine UK clinical practice.[175] The magnitude of the reduction was estimated by comparing survival times for patients who received subsequent treatments in MajesTEC-1 which are not routinely available in the UK (N=[redacted]), versus patients who received subsequent treatments which are routinely available in the UK (N=[redacted]), 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. The resulting acceleration factor was then used to 'shrink' the survival times of patients receiving non-routine subsequent treatments. The limited number of patients (N=[redacted]) who did receive subsequent treatments in line with UK clinical practice represents an unavoidable limitation of the subsequent treatment adjustment methodology.

The results of the subsequent treatment adjustment are presented in Table 38 and Table 39, which show the statistical fit of each of the extrapolation to the subsequent treatment adjusted OS KM data, and the long-term estimates of survival associated with each of the extrapolations, respectively. The corresponding smoothed hazard profiles are presented in Figure 39.

Table 38: Goodness-of-fit statistics for teclistamab OS extrapolations (including 2 stage OS adjustment)

Survival model	Teclistamab			
	AIC	BIC	AIC Rank	BIC Rank
Generalised Gamma	**1517.2**	1526.5	1	2
Lognormal	1517.4	**1523.6**	2	1
Loglogistic	1522.2	1528.4	3	3
Gompertz	1522.6	1528.8	4	4
Weibull	1526.6	1532.8	5	5

Gamma	1528.2	1534.4	6	6
Exponential	1531.7	1534.8	7	7

Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; PomDex: pomalidomide and dexamethasone.

Table 39: Comparison of predicted survival rates for teclistamab OS extrapolations (including 2 stage OS adjustment, with GPM cap)

Survival model	OS survival rates (%)			
	Teclistamab			
	Mean OS (months)	5 years	10 years	15 years
Clinical Expert Estimates				
Clinical expert estimates	NA	12–30%	5–15%	1–5%
Extrapolations				
Gompertz	75.8	28.91%	24.78%	19.96%
Generalised Gamma	65.4	27.96%	19.22%	14.95%
Loglogistic	52.1	23.18%	13.21%	9.26%
Lognormal	51.6	23.74%	13.09%	8.69%
Weibull	34.5	17.90%	5.02%	1.60%
Gamma	31.9	16.22%	3.38%	0.74%
Exponential	28.4	12.08%	1.45%	0.17%

Abbreviations: NA: not applicable; OS: overall survival; PomDex: pomalidomide and dexamethasone.

Figure 39. Hazard plot for OS, teclistamab, sATC(n=5), OS shrunk from the first non-UK treatment onwards

Source: Janssen. Data on file. Analysis based on MajesTEC-1 Clinical Study Report (August 2023 DCO).
Abbreviations: DCO: data cut-off; OS: overall survival; sATC: scaled average treatment effect for the control.

Table 38 shows that the lognormal and Generalised gamma extrapolations continued to provide the best statistical fit to the subsequent treatment adjusted OS KM data according to AIC and BIC respectively. Similar to the unadjusted data, of the two curves, the lognormal extrapolation was more closely aligned with the UK clinical expert estimates of survival and would be considered more clinically plausible.

A comparison of Table 39 with Table 41 shows that the subsequent treatment adjustment resulted in slightly lower long-term estimates of survival. For the log-normal, 10-year survival reduced from 14.00% to 13.09% with 15-year survival reducing from 9.30% to 8.69%. While these survival estimates were more conservative than the unadjusted lognormal, the 15-year survival estimate remained slightly above the upper end of the range provided by the clinical experts.

The only extrapolation to fall within the clinical expert estimates of survival at both 10 and 15 years was the Weibull extrapolation – however, the Weibull extrapolation produced amongst the worst statistical fits to the observed MajesTEC-1 data. Considering the other extrapolations, all survival curves generated estimates within the clinical experts 5-year survival range. However, at 10 years, the exponential was too pessimistic, and all other extrapolations were too optimistic versus the long-term estimates of survival except for the log-logistic, which fell within the range at 10 years but was too optimistic at 15 years, similar to the lognormal. Therefore, 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.

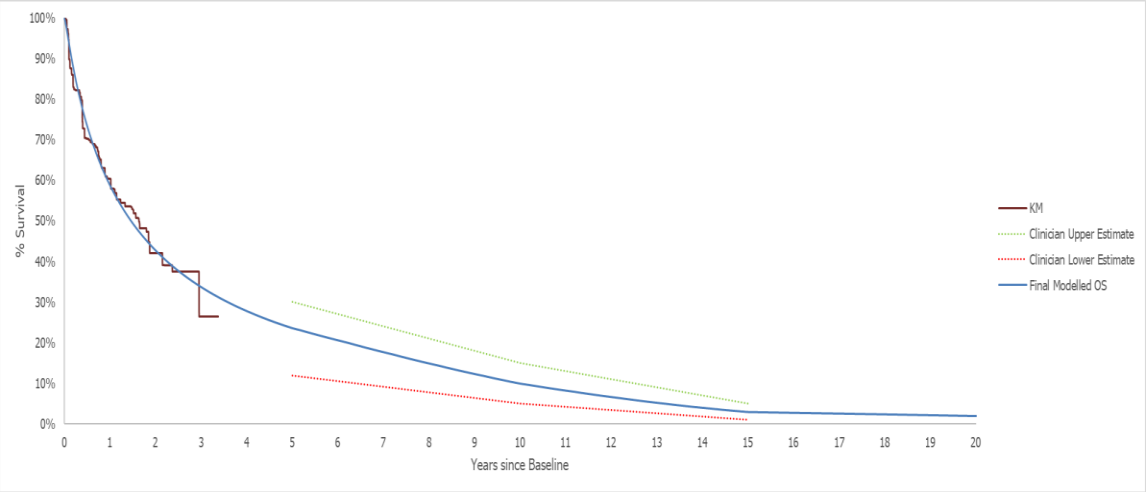
Therefore, the extrapolation which provided the best statistical fit to the observed data from MajesTEC-1 and fell within the 5- and 10- year range provided by the clinicians (i.e., lognormal) was taken forward and calibrated to align the subsequent-treatment adjusted 10- and 15- year lognormal extrapolation with 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.

Derivation of a calibrated lognormal extrapolation for teclistamab OS

Initially, it was necessary to consider when to start calibration of the lognormal extrapolation. Over three years of follow-up data were available from MajesTEC-1, with a median follow-up of 30.4 months and a longest follow-up of [redacted] months at the time of the latest DCO, suggesting that the lognormal extrapolation should not be adjusted any earlier than this.[105] With regard to long-term survival, both the five and ten-year OS estimates for the adjusted lognormal extrapolation (23.74% and 13.09%), were broadly aligned with the UK clinical expert estimates of survival at 5 years (range: 12% to 30%) and 10 years (ranging between 5% to 15%). Therefore, it was not considered necessary to calibrate the lognormal extrapolation any earlier than five years.

After Year 5, an attenuation factor was derived using a standardised mortality ratio factor applied to the general population mortality, of which further details can be found in Appendix N. The attenuation factor was therefore applied to the log-normal extrapolation to increase the hazard of death in each cycle after Year 5 so that the log-normal resulted in a 10-year survival of 10% (the midpoint of the clinical expert estimated 5–15%) and a 15-year survival of 3% (the midpoint of the clinical expert estimated 1–5%). The resulting extrapolation presented in Figure 40 thus provides 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.

Figure 40: Attenuated log-normal extrapolation fitted to the subsequent treatment adjusted OS KM data from MajesTEC-1



*clinical expert feedback sought at 5-, 10- and 15- year timepoints

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

In order to explore the uncertainty around the base case approach, alternative scenario analyses were explored, where the log-normal curve was attenuated to meet the upper and lower ranges of the UK clinical expert estimates of survival, instead of the midpoints:

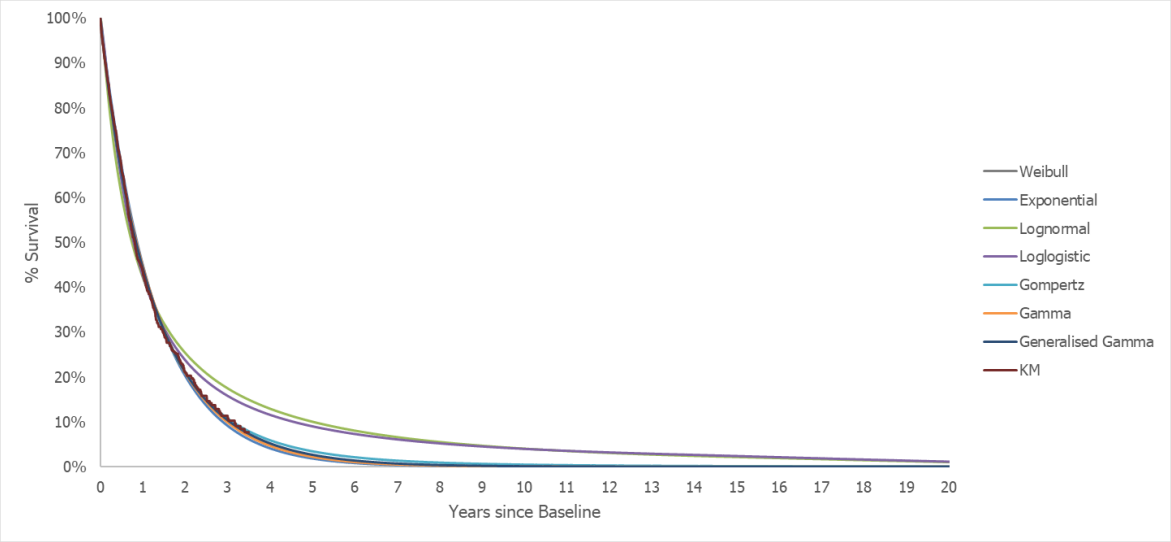
- Upper Limit: 15% OS at 10 years and 5% OS at 15 years
- Lower limit: 5% OS at 10 years and 1% OS at 15 years

The results of these scenario analyses are presented in Section B.3.11.3. Finally, it is important to note that, as detailed in Section B.2.10.2, the MajesTEC-1 trial occurred during the height of the COVID-19 pandemic before widespread access to COVID-19 vaccinations or treatments. UK clinical experts highlighted this as a key consideration for contextualising results of the trial and subsequent implications on this submission. While it is not possible to quantitatively adjust for the impact of COVID-19 excess mortality, it is highly likely that the observed OS data from MajesTEC-1 underestimate the true survival that would be observed for teclistamab patients in current UK clinical practice.[176]

PomDex

Extrapolations were fitted to the OS data for PomDex from the UK RW TCE cohort study, as previously presented in Section B.2.9. Despite the RWE TCE study including some subsequent treatments which are not reimbursed in the UK, as a conservative simplifying assumption, adjustment for subsequent treatment not reimbursed in the UK was not applied to the survival data for PomDex. Each of the OS extrapolations are presented in Figure 41, with goodness-of-fit statistics for each of the OS extrapolations presented in Table 40. Long-term estimates of OS for each parametric extrapolation are provided in Table 41. A smoothed hazard plot for PomDex OS is presented in Figure 42.

Figure 41: Extrapolation of OS for PomDex using IPD from the UK RW TCE study



Abbreviations: IPD: individual patient data; OS: overall survival; UK: United Kingdom.

Table 40: Goodness-of-fit statistics for PomDex OS extrapolations

Survival model	PomDex			
	AIC	BIC	AIC Rank	BIC Rank
Gompertz	**6615.7**	6624.6	1	2
Weibull	6616.2	6625.1	2	3
Exponential	6616.3	**6620.8**	3	1
Gamma	6616.5	6625.4	4	4
Generalised Gamma	6618.0	6631.4	5	5
Loglogistic	6636.9	6645.8	6	6
Lognormal	6674.6	6683.6	7	7

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival; PomDex: pomalidomide and dexamethasone.

Table 41: Comparison of predicted survival rates for PomDex OS extrapolations

Survival model	OS survival rates (%)			
	PomDex			
	Mean OS (months)	5 years	10 years	15 years
Clinical expert estimates				
Clinical expert estimates	NA	5-15%	0-5%	0-1%
Extrapolations				
Lognormal	24.48	10.10%	4.06%	2.18%
Loglogistic	24.07	9.06%	4.01%	2.41%
Gompertz	16.37	3.49%	0.48%	0.15%
Generalised Gamma	15.65	2.72%	0.11%	0.01%
Weibull	15.52	2.47%	0.08%	0.00%
Gamma	15.40	2.26%	0.06%	0.00%
Exponential	15.17	1.88%	0.03%	0.00%

Abbreviations: OS: overall survival; PomDex: pomalidomide and dexamethasone.

Figure 42. Hazard plot for OS, PomDex ECOG 0/1 cohort, sATC (n=5)

Source: Janssen. Data on file. UK RW TCE Cohort Study.
Abbreviations: DCO: data cut-off; ECOG: Eastern European Oncology Group; OS: overall survival; PomDex: pomalidomide plus dexamethasone; sATC: scaled average treatment effect for the control; TTD: time to discontinuation.

The Gompertz and exponential extrapolations provided the best statistical fit according to AIC and BIC respectively. However, it should be noted that given the relative maturity of the PomDex data from the UK RW TCE cohort study, all of the extrapolations were associated with a similar statistical fit (and similar long-term survival outcomes), with the exceptions of the loglogistic and lognormal extrapolations.

UK clinical experts predicted that between 0–5% of patients would be alive at 10 years, and 0–1% of patients would be alive at 15 years following treatment with PomDex. Of the two best fitting curves, the Gompertz extrapolation was more aligned with these estimates and therefore based on both high internal and external validity, was selected in the base case economic analysis. The decreasing hazards associated with the Gompertz extrapolation also appeared to track more closely with the smoothed hazard profile for PomDex and appeared more clinically plausible than the constant hazards associated with the exponential extrapolation. The exponential extrapolation was considered in a scenario analysis (Section B.3.11.3).

B.3.3.3 Progression-free survival

Teclistamab

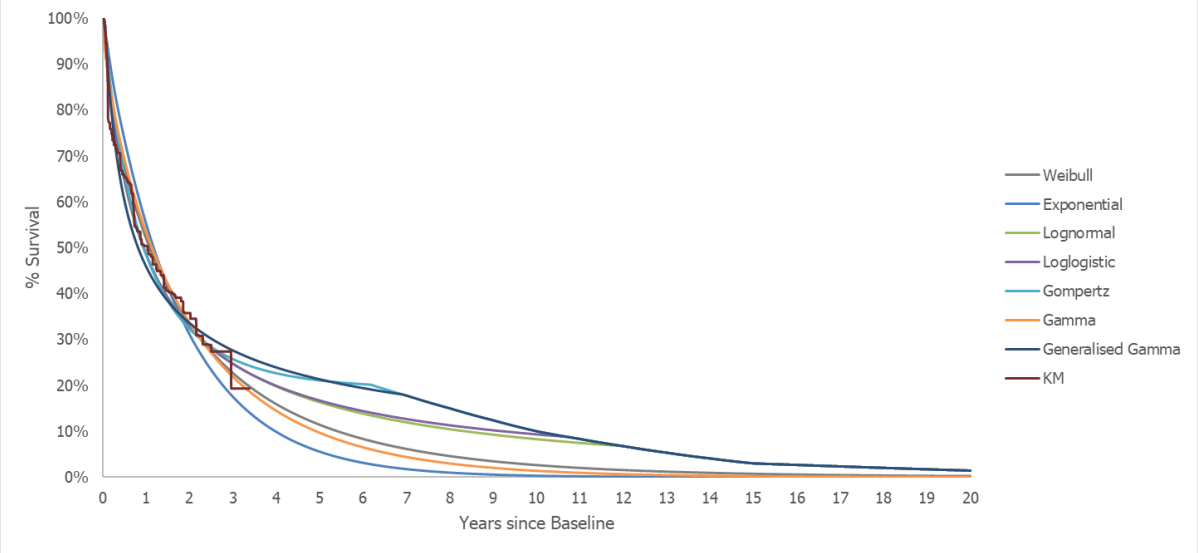
Company evidence submission template for teclistamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID6333]

Internal and external validity of the standard parametric extrapolations for teclistamab PFS

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 previously detailed in Section B.2.9. The PFS extrapolations implemented in the model include a cap to ensure that PFS did not exceed OS for teclistamab (as detailed in the previous section) to ensure clinical plausibility.

Each of the PFS extrapolations are presented in Figure 43 below, with goodness-of-fit statistics for each of the PFS extrapolations presented in Table 42. Long-term estimates of PFS for each parametric extrapolation are provided in Table 43.

Figure 43: Extrapolation of PFS for teclistamab using IPD from MajesTEC-1 (using TTNT as a proxy; adjusted via IPTW using ATC weights to align with the UK RW TCE cohort study)



Abbreviations: ATC: average treatment effect in the control; IPD: individual patient data; IPTW: inverse probability of treatment weighting; PFS: progression-free survival.

Table 42: Goodness-of-fit statistics for teclistamab PFS extrapolations

Survival model	Teclistamab			
	AIC	BIC	AIC Rank	BIC Rank
Generalised Gamma	**1699.7**	1709.0	1	2
Lognormal	1701.8	**1708.0**	2	1
Loglogistic	1708.7	1714.9	3	3
Gompertz	1711.9	1718.1	4	4
Weibull	1714.2	1720.4	5	5
Gamma	1717.1	1723.4	6	6
Exponential	1727.6	1730.7	7	7

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival; PomDex: pomalidomide and dexamethasone.

Table 43: Long-term PFS estimates for teclistamab PFS extrapolations (with OS cap)

Survival model	Proportion of patients progression-free (%)			
	Teclistamab			
	Mean PFS (months)	5 years	10 years	15 years
Clinical expert estimates				
Clinical expert estimates	NA	7–20%	2–8%	0–2%
Extrapolations				
Gompertz	37.3	21.11%	10.05%	3.02%
Generalised Gamma	37.2	21.36%	10.05%	3.02%
Loglogistic	34.2	16.74%	9.34%	3.02%
Lognormal	33.6	16.38%	8.30%	3.02%
Weibull	25.5	11.47%	2.65%	0.74%
Gamma	23.6	9.73%	1.40%	0.21%
Exponential	20.6	5.61%	0.32%	0.02%

Footnotes: The survival percentages include a cap such that PFS cannot exceed the teclistamab OS curve previously detailed in Section B.3.3.2.
Abbreviations: PFS: progression-free survival; PomDex; pomalidomide and dexamethasone.

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. All of the other extrapolations were at least 2 AIC points and 5 BIC points higher than the Generalised Gamma and lognormal extrapolations, indicating that they provided a statistically significantly worse fit to the observed data in MajesTEC-1.[173, 174]

UK clinical experts estimated that PFS for teclistamab would range between 2–8% at 10 years, and 0–2% at 15 years. Out of the two best fitting PFS extrapolations, the lognormal extrapolation provided the most clinically plausible long-term PFS estimates, with a 10-year PFS of 8.30% and a 15 year PFS of 3.02%, slightly exceeding the clinical expert estimates in both cases, while the 10-year PFS estimate associated while the Generalised Gamma was more optimistic and therefore not considered clinically plausible. Of the other extrapolations, the Weibull was the only extrapolation to provide long-term estimates of PFS that were aligned with the clinical expert estimates at 10 and 15 years, but the Weibull was associated with significantly worse statistical fit to the observed data from MajesTEC-1, when compared to the best fitting lognormal and generalised gamma extrapolations.

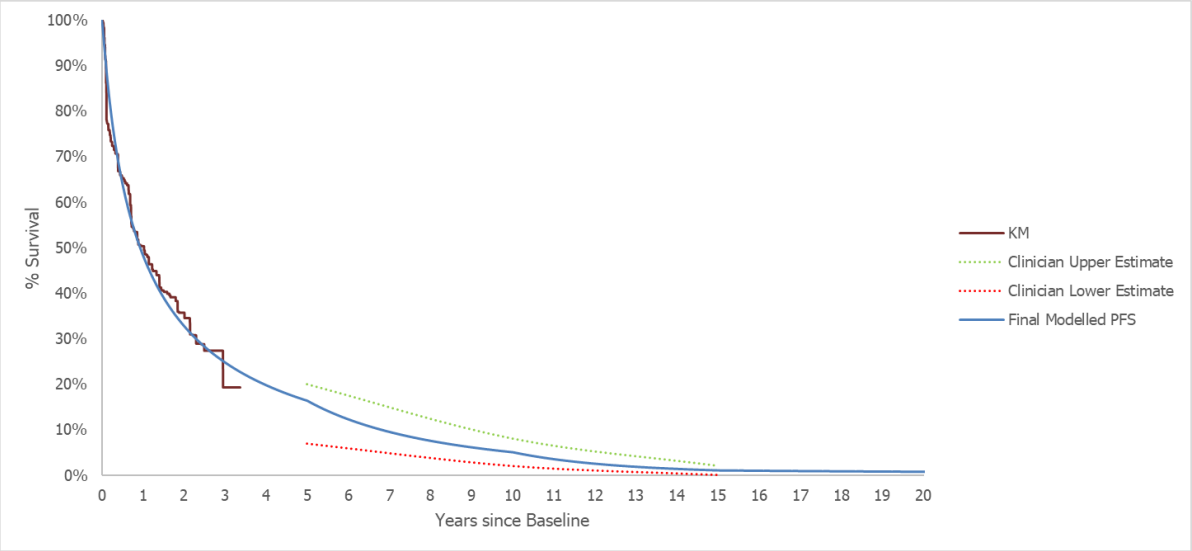
As such, similar to OS, when considering both statistical fit and long-term clinical plausibility, none of the generated extrapolations appear to be suitable for use in the base case economic analysis.

Derivation of a calibrated lognormal extrapolation for teclistamab PFS

As such, in line with the approach taken for OS, after Year 5, an attenuation factor was applied to the log-normal 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 adjusted lognormal PFS

extrapolation is presented in Figure 44 below, showing both high internal validity with the best statistical fit to the observed MajesTEC-1 PFS data, while also ensuring that the long-term PFS extrapolations are consistent with clinical expert estimates.

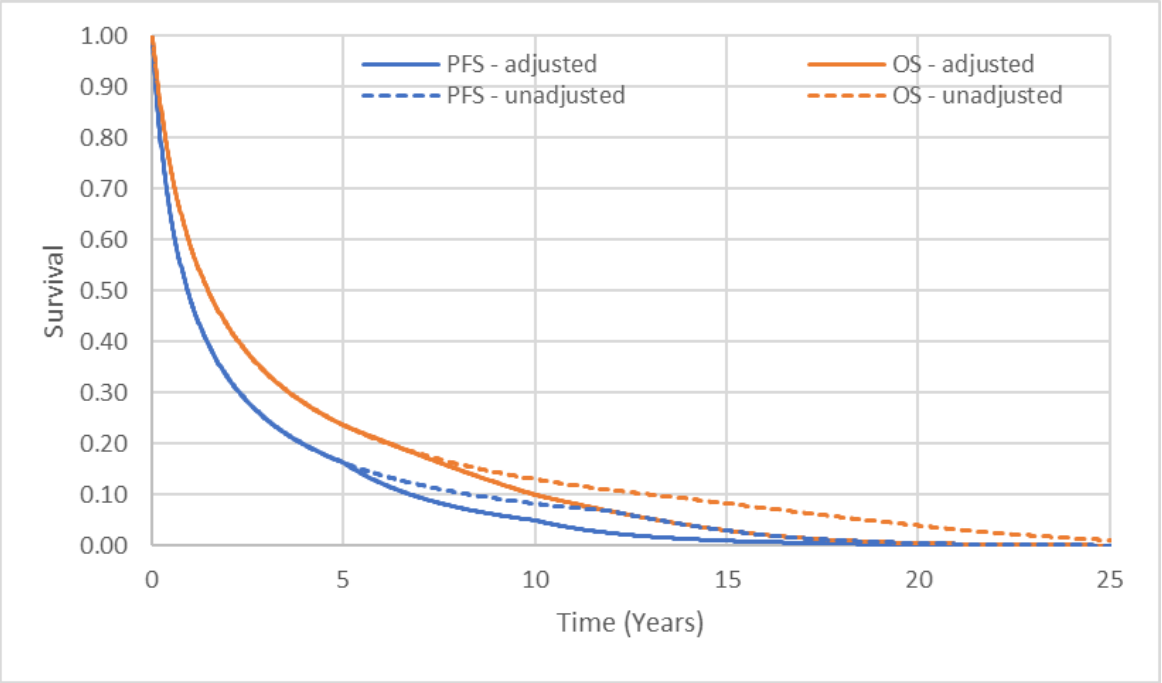
Figure 44: Attenuated log-normal extrapolation fitted to the PFS KM data from MajesTEC-1



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

The uncalibrated and clinical expert calibrated PFS and OS extrapolations for teclistamab overlaid on the same graph are presented in Figure 45. This figure highlights the effects of the calibrations used in the base case economic analysis which provides lowered OS and PFS extrapolations when compared to using the original uncalibrated curves.

Figure 45: Summary of calibrated PFS and OS log-normal extrapolations



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

In order to explore the uncertainty around the base case approach, alternative scenario analyses were explored, where the log-normal curve was attenuated to meet the upper and lower ranges of the UK clinical expert estimates of survival, instead of the midpoints:

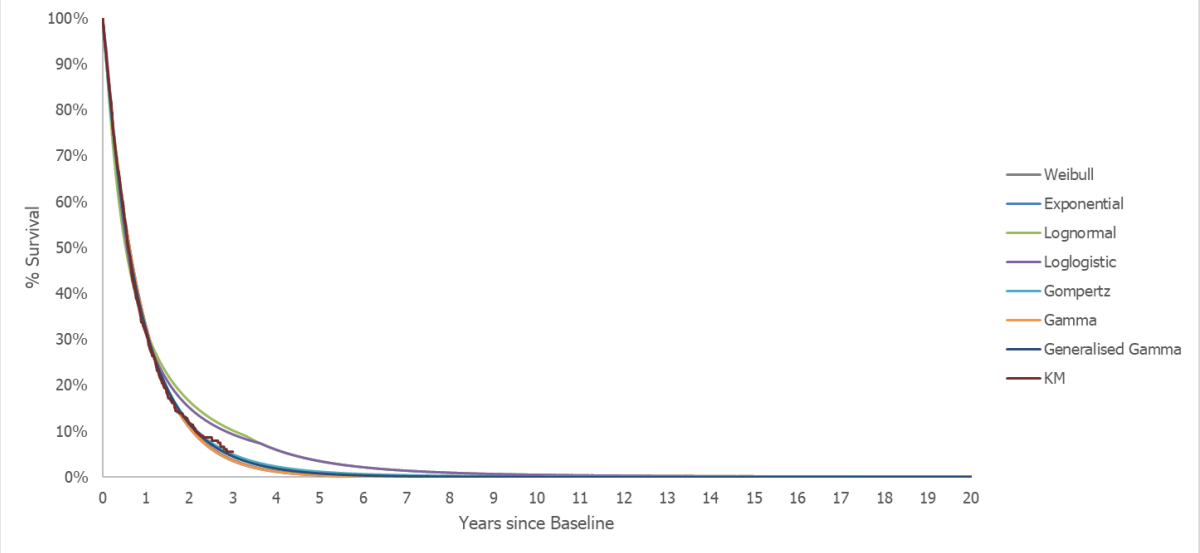
- Upper Limit: 8% PFS at 10 years and 2% PFS at 15 years
- Lower limit: 2% PFS at 10 years and 0% PFS at 15 years

As previously detailed in Section B.2.9, as TTNT and PFS data observed in MajesTEC-1 were highly consistent, the use of TTNT as a proxy for PFS should not be considered to represent a major source of uncertainty. However, in order to address any uncertainty relating to the use of TTNT as a proxy for PFS, alternative scenario analyses were conducted where PFS data for teclistamab from the MajesTEC-1 trial (measured by either IRC or INV) were used instead of TTNT, as detailed in Section B.3.11.3.

PomDex

In the absence of PFS data, extrapolations were fitted to the TTNT data (as a proxy for PFS) for PomDex from the UK RW TCE cohort study, as previously presented in Section B.2.9. Each of the PFS extrapolations are presented in Figure 46 below, with goodness-of-fit statistics for each of the PFS extrapolations presented in Table 44. Long-term estimates of PFS for each parametric extrapolation are provided in Table 45. As with teclistamab, the PFS extrapolations presented include a cap to ensure that PFS did not exceed OS for PomDex.

Figure 46: Extrapolation of PFS for PomDex using IPD from the UK RW TCE cohort study



Note: Extrapolations shown are with the OS cap applied
Abbreviations: IPD: individual patient data; PFS: progression-free survival; PomDex: pomalidomide and dexamethasone.

Table 44: Goodness-of-fit statistics for PomDex PFS extrapolations

Survival model	PomDex			
	AIC	AIC	AIC Rank	BIC Rank
Gompertz	**6926.3**	6935.2	1	2
Exponential	6927.4	**6931.9**	2	1
Generalised Gamma	6928.6	6942.0	3	5
Weibull	6929.2	6938.1	4	3
Gamma	6929.4	6938.4	5	4
Loglogistic	6943.2	6952.1	6	6
Lognormal	6982.8	6991.8	7	7

Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival; PomDex: pomalidomide and dexamethasone.

Table 45: Comparison of predicted survival rates for PomDex PFS survival models (with OS cap)

Survival model	Proportion of patients progression-free (%)			
	PomDex			
	Mean PFS (months)	5 years	10 years	15 years
Clinical expert estimates				
Clinical expert estimates	NA	2-10%	0-5%	0-0%
Extrapolations				
Lognormal	13.82	3.49%	0.48%	0.15%
Loglogistic	13.69	3.49%	0.48%	0.15%

Gompertz	11.45	1.18%	0.12%	0.04%
Generalised Gamma	11.14	0.79%	0.02%	0.00%
Weibull	10.91	0.45%	0.00%	0.00%
Exponential	10.86	0.38%	0.00%	0.00%
Gamma	10.86	0.39%	0.00%	0.00%

Abbreviations: PFS: progression-free survival; PomDex; pomalidomide and dexamethasone.

The Gompertz and Exponential extrapolations provided the best statistical fit to the observed data according to AIC and BIC, respectively. With the exception of the log-logistic and log-normal extrapolation, all of the extrapolations were associated with similar statistical fits. Generally, all of the curves were aligned with the UK clinical expert estimates of survival at 10 and 15 years.

Of the two best fitting extrapolations, the Gompertz extrapolation was preferred to the exponential in the base case analysis as the Gompertz is more closely aligned with UK clinical expert's estimates of PFS. The use of the exponential is explored in a scenario analysis.

B.3.3.4 Time to treatment discontinuation

Teclistamab

In order to model treatment duration for teclistamab, extrapolations were fitted to TTD data from MajesTEC-1, as presented in Figure 47. Goodness-of-fit statistics for each of the TTD extrapolations are presented in Table 46, and long-term estimates of TTD for each parametric extrapolation are provided in Table 47. The TTD extrapolations included a cap to ensure that TTD does not exceed the PFS extrapolation for teclistamab detailed in Section B.3.3.3 at any given point.

Figure 47: Extrapolation of TTD for teclistamab using IPD from MajesTEC-1

Footnote: In the model, TTD is capped by PFS.
Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to discontinuation.

Table 46: Goodness-of-fit statistics for teclistamab TTD survival models

Survival model	Teclistamab			
	AIC	BIC	AIC Rank	BIC Rank
Lognormal	**1854.4**	**1860.6**	1	1
Generalised Gamma	**1854.4**	1863.7	1	2
Loglogistic	1862.1	1868.3	3	3
Weibull	1865.3	1871.5	4	4
Gompertz	1866.3	1872.5	5	5
Gamma	1868.1	1874.3	6	6
Exponential	1878.9	1882.0	7	7

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to discontinuation.

Table 47: Comparison of predicted estimates for teclistamab TTD extrapolations

Survival model	Patients on treatment (%)			
	Teclistamab			
	Mean TTD (months)	5 years	10 years	15 years
Clinical expert estimates				
Clinical expert estimates	NA	4-20%	1-5%	0-2%
Extrapolations				
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; PomDex: pomalidomide and dexamethasone.

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.

The three remaining curves were all associated with broadly similar estimates of long-term survival, only differing by [redacted]% at 10 years, and [redacted]% at 15 years. All three extrapolations were aligned with the UK clinical expert estimates of long-term TTD at 5-years and 15-years; at 10 years, the Gamma and Exponential extrapolations slightly underestimated TTD, but fell <1% outside the range of expert estimates. Therefore, these three extrapolations were all considered to be plausible.

Unlike PFS and OS, as three extrapolations were all considered to be clinically plausible, as well as providing a reasonable visual fit to the observed TTD data from MajesTEC-1, it was not considered necessary to adjust the TTD extrapolations to ensure long-term clinical plausibility.

As such, given the similarity of the three curves, the Gamma extrapolation was selected as the midpoint of the three remaining curves that were potentially clinically plausible – the Weibull extrapolation was explored in a scenario analysis.

PomDex

TTD data for PomDex were not available from the UK RW TCE cohort study. PomDex is a treat until progression regimen and therefore it could be assumed that PFS can be used a proxy for treatment duration. However, this may overestimate the costs of PomDex. In order to be as conservative as possible, and to align with the use of a separate TTD curve for teclistamab, the relative difference between teclistamab PFS (using TTNT as a proxy) and teclistamab TTD was calculated; the resulting HR was applied to the Gompertz PomDex PFS extrapolation to derive a TTD extrapolation for PomDex. The resulting PomDex TTD extrapolation is presented in Figure 48.

Figure 48: PomDex TTNT KM and extrapolation overlaid with the derived TTD curve

Abbreviations: KM: Kaplan-Meier; PomDex: pomalidomide and dexamethasone; TTNT: time to next treatment; TTD: time to treatment discontinuation.

B.3.3.5 Teclistamab dose switching

As outlined in Section B.1.2, the SmPC for teclistamab states that in patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg SC every two weeks may be considered.[139]

In order to model the proportion of patients switching from a QW to Q2W dose of teclistamab, an additional dose switching curve is implemented in the model. Out of all of the patients remaining on treatment in a given cycle, this additional curve calculates the proportion of those who have switched to Q2W dosing over time. Time to event is defined as the earliest of death,

discontinuation, and switch to a Q2W dosing. The remaining patients on treatment are assumed to remain on a QW dosing regimen.

The dose switching KM data are taken directly from the MajesTEC-1 trial, and in line with the approaches to PFS, OS and TTD, parametric extrapolations were fitted to the KM data of patients switching from a QW to Q2W dosing regimen of teclistamab in the MajesTEC-1 trial. In the trial, 65 patients switched to a Q2W dosing regimen, with a median time to switch of [redacted] months (95% CI: [redacted], [redacted]).

As the KM data from MajesTEC-1 for dose switching were complete i.e., all patients remaining on treatment switched away from a QW dose, it would have been possible for the KM data to be implemented directly into the cost-effectiveness model. However, in order to smooth out the occurrence of dose switching events, compared to the stepwise nature of the KM data, the use of standard parametric extrapolations fitted to the observed dose switching KM data was considered preferable to using the KM data directly.

Goodness-of-fit statistics for each parametric distribution explored are presented in Table 46 and the extrapolations are presented in Figure 47 for teclistamab. As the KM data for dose switching from MajesTEC-1 are mature, it was deemed appropriate to select the Gompertz extrapolation to model dose switching for teclistamab in the base case economic model as it has the best statistical fit.

Scenario analyses

Feedback received from UK clinical experts consulted during several validation meetings in December 2023 highlighted that clinicians would want to switch patients onto a less frequent dose of teclistamab as soon as they are eligible.[176] Additionally, it was noted that patients would likely want to switch onto a less frequent dosing schedule as soon as feasible, owing to their preference for treatments associated with a reduced administrative burden and their preference for treatments providing 'longer remission/treatment-free periods' [74].

Per the teclistamab SmPC, patients must be in CR for 6 months before being eligible for dose switching, and the median/mean times to CR or better in MajesTEC-1 were [redacted] months and [redacted] months, respectively. It was therefore assumed that patients in UK clinical practice will be eligible to switch to Q2W dosing after 1 year of treatment. As such, a scenario analysis was included in the model whereby all patients remaining on treatment with teclistamab after one year were assumed to switch to the Q2W dosing (see Section B.3.11.3). This scenario aimed to more accurately reflect the fact that patients receiving teclistamab in UK clinical practice may receive Q2W dosing as soon as feasible owing to both patient and clinician preferences.

Table 48: Goodness-of-fit statistics for teclistamab TTD (with dose switching) survival models

Survival model	Teclistamab			
	AIC	BIC	AIC Rank	BIC Rank
Gompertz	**2,151.4**	**2,157.6**	1	1
Generalised Gamma	2,152.1	2,161.4	2	2
Weibull	2,159.3	2165.5	3	4
Gamma	2,161.1	2,167.3	4	5
Exponential	2,162.3	2,165.4	5	3
Lognormal	2,184.2	2,190.4	6	6
Loglogistic	2,195.7	2,201.9	7	7

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to discontinuation.

Figure 49: Extrapolation of dose switching for teclistamab using IPD from MajesTEC-1

Abbreviations: IPD: individual patient data; KM: Kaplan-Meier; PFS: progression-free survival; TTD: time to discontinuation.

B.3.3.6 Summary of survival approaches

An overview of the approaches used to model OS, PFS and TTD for teclistamab and PomDex, as well as dose switching for teclistamab only in the base case cost-effectiveness analysis are presented in Table 49.

Table 49: Summary of base case survival approaches

	Teclistamab	PomDex
PFS[a]	Calibrated Log-Normal[b]	Gompertz
OS	Calibrated Log-Normal[c]	Gompertz
TTD	Gamma	HR between PFS and TTD for teclistamab is applied to the PomDex PFS extrapolation
QW to Q2W dose switching	Gompertz	NA

Footnotes: [a] Based on TTNT as a proxy; [b] Calibrated after 5 years to result in 10-year PFS of 5% and 15-year PFS of 1% in line with clinicians' survival estimates. [c] Calibrated after 5 years to result in 10-year OS of 10% and 15-year OS of 3% in line with clinicians' survival estimates.
Abbreviations: OS: overall survival; PFS: progression-free survival; PomDex: pomalidomide and dexamethasone; TTD: time to treatment discontinuation.

B.3.3.7 Adverse events

AEs for teclistamab were informed by the MajesTEC-1 trial. For PomDex, AE data were not collected in the UK RW TCE cohort study, and no studies were identified in the clinical SLR that reported results for PomDex in a patient population with TCE RRMM. Thus, in the base case economic analysis, AEs for PomDex were informed by the MM-003 trial, a published source of AE data for PomDex accepted as part of TA338/427.[8, 38] The MM-003 trial does not directly align with the patient population of interest for this submission, as MM-003 only required patients to have received two prior therapies (including lenalidomide (ImiD) and bortezomib (PI)) and no requirement to be TCE. [85] This could mean that the trial potentially underestimates the Aes that would be associated with PomDex for patients with RRMM after at least three prior therapies.

Grade ≥3 AEs that had occurred in at least 5% of patients for either teclistamab (in the MajesTEC-1 trial) or PomDex (in the MM-003 trial) were included in the economic model. The inclusion rule that events must have occurred in at least 5% of patients in either trial was selected to capture Aes that would impact patients consistently enough to have validity in a real-world setting where Aes are monitored in a less strict manner compared with a clinical trial setting. As CRS and neurotoxicity are adverse events of special interest (AESIs) associated with teclistamab, Grade 1–2 events were included in addition to Grade 3+, and no minimum incidence criteria were applied.

The AE rates included in the economic model are presented in Table 50. The disutilities associated with Aes are presented in Section B.3.4.4, and the costs associated with the management of Aes are presented in B.3.5.3.

Table 50: Summary of AEs included in the economic model

AE	Teclistamab	PomDex
Anaemia	37.6%	32.7%
Asthenia and fatigue	[redacted]	9.0%
CRS, Grade 1–2	71.5%	0.0%
CRS, Grade 3+	0.6%	0.0%
Dyspnoea	0.0%	5.0%
Febrile neutropenia	[redacted]	9.3%
Hypertension	[redacted]	0.0%
Hypophosphatemia	[redacted]	0.0%
Leukopenia	9.1%	9.0%
Lymphopenia	34.5%	0.0%
Neurotoxicity, Grade 1-2	[redacted]	0.0%
Neurotoxicity, Grade 3+	[redacted]	0.0%
Neutropenia	65.5%	48.3%
Pneumonia	[redacted]	12.7%
Thrombocytopenia	23.0%	22.0%
Source	MajesTEC-1 (August 2023)[105]	MM-003 (TA338/427)[85]

Abbreviations: AE: adverse event; PomDex: pomalidomide and dexamethasone.

B.3.4 *Measurement and valuation of health effects*

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

In the MajesTEC-1 trial, patients in the Phase 2 part of the study completed PRO measures related to their HRQoL, including the EORTC-QLQ-C30, Patient Global Impression of Severity (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 even cycle during treatment (i.e., Day 1 of Cycles 2, 4, 6, 8, 10 etc.),
- Every 16 weeks (±2 weeks) post initial indication of progressive disease or end of treatment (whichever occurred first)

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 MajesTEC-1 are provided in Section B.2.6.8.

B.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 MajesTEC-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).[167-169] The resulting utility values for teclistamab derived from the mapping are presented in Section B.3.4.5.

B.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 H).

Of the 166 publications, encompassing 118 unique studies, that met the SLR inclusion criteria, 12 studies reported direct utility values for the TCE RRMM population. These studies comprised one randomised trial (CC-220-MM-001), five non-randomised trials (CARTITUDE-1, HORIZON, KarMMA, MajesTEC-1, and MonumenTAL-1), and one observational study (Connect MM). With the exception of MajesTEC-1, the majority of these studies included treatments which are not available in UK clinical practice and therefore were not considered relevant for the economic model.

Therefore, the MajesTEC-1 trial was considered to represent the most appropriate source of health state utility values for teclistamab, as further detailed in Section B.3.4.5.

In the absence of utility data for PomDex in RRMM patients after at least three prior therapies, alternative sources were considered. In a recent NICE appraisal in RRMM, PomDex utility values were informed by the MM-003 trial (TA510[38]/TA783).[8] As such, the accepted utility values used in TA510 were considered to represent the most appropriate source of health state utility values for PomDex in the economic model.

Further details on the incorporation of the health state utility values in the base case economic analysis can be found in Section B.3.4.5.

B.3.4.4 Adverse reactions

One-off decrements in utility were applied in the model for the proportion of patients who experienced TEAEs, based on the duration of AEs informed by the latest DCO of the MajesTEC-1 trial and a utility decrement for each AE based on the published literature. The disutility for Grade 1–2 CRS events was informed by the CARTITUDE-1 trial for cilta-cel, and it was assumed that patients experiencing Grade 3+ CRS would have a utility equal to zero for the duration of the event.

A summary of the AE disutilities included in the base case economic analysis is presented in Table 51.

Table 51: Summary of AE disutilities included in the economic model

Adverse event	Utility decrement	Decrement sources	Duration of AE (days)	Duration sources	Overall QALY loss per AE
Anaemia	-0.3100	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]	MajesTEC-1 (August 2023 DCO)[105]	[redacted]
Asthenia and fatigue	-0.1150	Lloyd 2006[178]	[redacted]		[redacted]
CRS, Grade 1–2	-0.1109	CARTITUDE-1	[redacted]		[redacted]
CRS, Grade 3+	[redacted]	Patients with Grade 3+ CRS are assumed to experience 0 quality of life	[redacted]		[redacted]
Dyspnoea	-0.0500	Doyle 2008[179]	[redacted]		[redacted]
Febrile neutropenia	-0.3900	TA510 (based on Launois et al. [1996])[180]	[redacted]		[redacted]
Hypertension	0.0000	TA573 (assume to be controlled by medication and therefore have no impact on HRQoL)[181]	[redacted]		[redacted]
Hypophosphatemia	-0.1500	TA559 (2018)[182]	[redacted]		[redacted]
Leukopenia	-0.0650	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]		[redacted]
Lymphopenia	-0.0650	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]		[redacted]
Neurotoxicity, Grade 1–2	0.0000	Assumed to be captured as part of CRS disutility	[redacted]		[redacted]
Neurotoxicity, Grade 3+	0.0000	Assumed to be captured as part of CRS disutility	[redacted]		[redacted]
Neutropenia	-0.1450	Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]		[redacted]
Pneumonia	-0.1900	Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]		[redacted]

Thrombocytopenia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar et al. [2014])[177]	[redacted]		[redacted]

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; QALY: quality adjusted life year; TA: technology appraisal.

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

To ensure an accurate representation of patient HRQoL, the base case economic analysis considered treatment-dependent health state utility values (HSUVs). This approach was deemed appropriate based on the distinct mechanism of action between teclistamab and PomDex which leads to highly differentiated depths of response (see Section B.2.12) and evidence from multiple studies demonstrating that MM treatments which drive a deeper response are associated with improvements in HRQoL. A SLR that explored the relationship between HRQoL and clinical response in MM patients, supports this observation, revealing that the almost all studies (12/14) reported enhanced patient HRQoL with deeper responses.[84] This association is clinically plausible since deeper responses indicate reduced myeloma cells, subsequently decreasing bone damage-related symptoms and intuitively improving HRQoL.

Teclistamab

Utility values for the progression-free (PF) and progressed-disease (PD) health states for teclistamab were derived using EQ-5D-5L data in the MajesTEC-1 trial, based on the cross-walk method reported by Hernández Alava et al. (2017) to map EQ-5D-5L dimension scores from the MajesTEC-1 trial to utilities using the UK EQ-5D-3L value set (Section B.3.4.2).[183]

PF health state

EQ-5D data collected during the MajesTEC-1 trial demonstrated that patient utility values improved with increasing time spent in the progression-free health state. As such, in the base case analysis utility values for PFS were modelled to be time-dependent based on PFS health state utility values estimated at each treatment cycle, as detailed in Table 52. Further methodological details on the derivation of these utility values can be found in Appendix M.

The use of time-dependent utilities in the base case analysis was supported by feedback from UK clinical experts in MM. They noted that time-dependent utility values were more appropriate given the observed initial decline in quality of life typically experienced by patients initiating treatment with teclistamab during the step-up dosing period, which correlated with active disease. Over the course of their treatment, as patients achieve progression-free health state, their quality of life tends to improve.[83]

This approach also reflects the evolving composition of the overall patient cohorts over time – with patients who fail to respond to treatment progressing more rapidly, while those who remain in a progression-free health state for extended periods experiencing the deepest and most durable treatment responses.

PD health state

Due to insufficient data in MajesTEC-1, the use of time-dependent HSUV in the PD health state could not be informed. As a result, a utility of [redacted] was applied uniformly across the PD health state. The decrease in utility for patients with PD embodies the dearth of effective subsequent treatment options in current UK clinical practice. It also encompasses the psychological and emotional burden that patients experience when they reach the end of the treatment pathway.

PomDex

As previously detailed in Section B.3.4.3, in the absence of PomDex utility data for patients with RRMM after at least three prior therapies, the Committee's accepted health state utility values used for PomDex in TA510[38]/TA783[8] were used to inform the health state utility values for PomDex in the base case analysis. It is important to note that these values represent a conservative assumption as they are derived from RRMM patients in the MM-003 trial rather than patients with triple-class exposed RRMM. This difference is of significance given the limited availability of novel, effective treatment options, patients with TCE RRMM bear a substantial symptomatic burden alongside heightened emotional distress (Section B.1.3.3).[66, 67] Consequently, patients with TCE RRMM are likely to experience a diminished health-related quality of life compared to the less heavily pre-treated patient population included in the MM-003 trial. Therefore, it is expected that these utility values slightly overestimate the HRQoL of patients with TCE RRMM in UK clinical practice.

Given the absence of data indicating the variability of utilities over time in patients treated with PomDex, time-independent HSUV for PF was modelled in the base case analysis for PomDex. The decision not to include time-dependent PF HSUVs for PomDex is considered appropriate given that the observed variations in utility over-time in the MajesTEC-1 trial being primarily associated with the deepening of responses. As previously detailed in Section B.2.6.3, the mean time to first response to teclistamab is [redacted] months, with a mean time to best response of [redacted] months and a mean time to CR or better of [redacted] months. In contrast, only a very small minority of patients receiving PomDex are likely to ever achieve CR. Consequently, a similar deepening of responses and subsequent improvement in HRQoL over time is unlikely with PomDex, making time-dependent utilities for the PF health state inappropriate.

Scenario analyses

In order to explore the impact of this conservative assumption for PomDex, a range of alternative utility scenario analyses were explored:

- Using the MajesTEC-1 *time-independent* health state utility for PFS for PomDex ([redacted]), alongside the time-dependent utilities for teclistamab, in the absence of data showing that HRQoL increases over time for patients receiving PomDex

- Using the MajesTEC-1 *time-dependent* health state utility values for PFS for both teclistamab and PomDex alongside the time independent health state utility value for PD. Given that, as noted above, deeper responses translate to improvements in HRQoL,, an assumption that teclistamab and PomDex would be associated with the same health state utility values is considered highly conservative

These scenarios are detailed further in Section B.3.11.3.[163]

In the model, HSUVs were also 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.[170]

A summary of the progression-free and progressed disease utility values used in the base case economic analysis for teclistamab is provided in Table 52 and Table 53, respectively. A summary of the HSUVs used in the base case analysis for PomDex are provided in Table 54.

Table 52: Summary of progression-free utility values for teclistamab used in the base case economic analysis

Time (number of 28-day cycles)	Utility	SE	Source
0	[redacted]	[redacted]	MajesTEC-1 (August 2023 DCO, CS model with the lowest AIC)
2	[redacted]	[redacted]	
4	[redacted]	[redacted]	
6	[redacted]	[redacted]	
8	[redacted]	[redacted]	
10	[redacted]	[redacted]	
12	[redacted]	[redacted]	
14	[redacted]	[redacted]	
16	[redacted]	[redacted]	
18	[redacted]	[redacted]	
20	[redacted]	[redacted]	
22	[redacted]	[redacted]	
24 or more	[redacted]	[redacted]	

Abbreviations: AIC: Akaike information criterion; CS: Correlation Structure; SE: standard error.

Table 53: Summary of progressed disease utility value for teclistamab used in the base case economic analysis

Utility	SE	Source
[redacted]	[redacted]	MajesTEC-1 trial (August 2023, CS model (the lowest AIC))

Abbreviations: SE: standard error.

Table 54: Summary of health state utility values for PomDex used in the base case economic analysis

Health state	Utility	SE	Source
PF	0.610	0.010	MM-003 (TA510[38]/TA783[8])
PD	0.570	0.010	

Abbreviations: SE: standard error.

B.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 I.

The health economic analysis was conducted from the perspective of the NHS in England and therefore only included costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2021–2022, 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 end-of-life palliative care

B.3.5.1 Intervention and comparator's cost and resource use

Drug acquisition costs

The drug acquisition costs for teclistamab and PomDex are presented in Table 55, based on their current list prices and licensed doses.

Dosing regimens for teclistamab and PomDex are shown in Table 56. Both the drug acquisition costs at list price and incorporating the simple PAS discount for teclistamab are provided. Janssen acknowledges that a simple PAS discount exists for pomalidomide, however as the discount is not publicly available, only the list price for PomDex is provided in Table 56.

The model included a proportion of doses/administrations of teclistamab being skipped, based on the MajesTEC-1 trial data. Of the [redacted] expected maintenance dose administrations in the MajesTEC-1 trial, [redacted] were skipped and not made up, resulting in [redacted] of teclistamab doses being skipped. In the model, dose skipping was applied for the maintenance doses only (from Cycle 2 onwards) given that none of the patients in MajesTEC-1 missed a step-up dose.

Additionally, in line with the MajesTEC-1 trial, a proportion of patients receiving teclistamab were modelled to switch from a QW to Q2W dosing schedule. This was determined by a separate dose switching parametric extrapolation, as previously detailed in Section B.3.3.4.

In the absence of equivalent data, dose skipping for PomDex was assumed to be 0%. Relevant data on dose intensity is not available from the UK RW TCE cohort study, but for consistency with previous appraisals, the dose intensity assumptions were aligned with those applied in the relevant appraisals. This is likely conservative as the trial populations used to inform these rates are likely fitter and younger than the UK TCE RRMM study population. The dose intensities used in the appraisal of PomDex (TA427) were based on the observation from the relevant trials that 3.59% of packs of PomDex were not distributed to patients due to dose interruption. Therefore, it was assumed the dose intensity was 100% less this value, i.e. 96.41%.[163]

Table 55: Summary of drug costs for teclistamab and PomDex

Intervention	Pack Size	Strength	Price per pack (£)	PAS Discount	Discounted price per pack	Source
Teclistamab	1	30 mg/3 ml solution for injection	£775.14	[redacted]	[redacted]	BNF
	1	153 mg/1.7 ml solution for injection	£3,952.78	[redacted]	[redacted]	BNF
Pomalidomide	21	4 mg capsules	£8,884.00	NA[a]	NA	BNF
Dexamethasone (oral)	50	2.0 mg	£2.62	NA	NA	eMIT 2023

Footnotes: [a]Janssen acknowledges that a simple PAS discount exists for pomalidomide, however as the discount is not publicly available, only the list price for pomalidomide is provided in the table
Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; NA: not applicable; PAS: Patient Access Scheme; PomDex: pomalidomide and dexamethasone.

Table 56: Summary of dosing regimens for front-line treatment included in the model

Treatment	Dosing regimen	Administrations per model cycle[a]	Source/Justification
Teclistamab			
Teclistamab (Step Up Dosing)	0.06 and 0.3 mg/kg in Week 1	2	Teclistamab SmPC
Teclistamab (QW dosing)	1.5 mg/kg once every week	1	Teclistamab SmPC
Teclistamab (Q2W dosing)	1.5 mg/kg once every two weeks	0.5	Teclistamab SmPC
PomDex			
Pomalidomide	4 mg daily for 3 weeks, followed by 1 week rest period	7	Pomalidomide SmPC
Dexamethasone	40 mg oral once weekly	1	Dexamethasone SmPC

Footnotes: [a]Every fourth model cycle, patients are modelled to take a 1-week rest period, during which they do not receive treatment with pomalidomide.
Abbreviations: CR: complete response; QW: once weekly; Q2W: once every two weeks; SmPC: Summary of Product Characteristics.

Drug wastage

As teclistamab dosage is weight-dependent, there is potential for drug wastage to occur if vial sharing is not practiced. In the base case economic analysis, it is assumed that vial sharing is prevalent, resulting in a conservative estimate of 15% wastage per vial. This approach aligns with the Committee's accepted approach to drug wastage in the NICE appraisal for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies (ID2701).[22] It should be noted that once reconstituted, the shelf life of teclistamab (20 hours) exceeds that of belantamab mafodotin (4 hours), suggesting that assuming 15% wastage may be conservative.[184]

During validation interviews with UK clinical experts to support this submission, it was emphasised that vial sharing is maximised in clinical practice, confirming that an assumption of 15% drug wastage may be on the conservative side.[83] Nevertheless, uncertainty around this assumption was explored in a scenario analysis exploring a higher drug wastage rate of 25% (see Section B.3.11.3).

Administration costs

The cost of administration was included for both fourth-line and subsequent therapies (Table 57). Given its oral method of administration, a one-off cost was applied on initiation of PomDex. In contrast, given teclistamab is administered subcutaneously, a cost was applied for each subcutaneous administration of teclistamab.

In addition to the administration costs associated with each dose of treatment, teclistamab requires an initial step-up dosing regimen. The teclistamab SmPC states that patients should remain within proximity of a healthcare facility, and should be monitored for signs and symptoms daily for 48 hours after administration of all step-up doses.[139] Therefore, each patient was modelled to spend 4 days in hospital in the first weekly cycle and 2 days in hospital in the second weekly cycle.[139] These hospitalisation costs, based on the cost of an inpatient stay per day of £695.72, are included in the drug administration costs for teclistamab.

Table 57: Summary of drug administration costs in the economic model

Administration	Cost	Source
Complex first IV infusion	£485.23	National Schedule of NHS Costs 2021–22, SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – Daycase and Regular Day/Night admissions + blood sample prior 1st infusion[185]
Other IV administration	£326.46	National Schedule of NHS Costs 2021–22, SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle – Outpatient[185]
Each SC administration	£119.00	National Schedule of NHS Costs 2021–22, N10AF: Specialist Nursing, Cancer Related, Adult, Face to face[185]
Oral drug initiation	£197.25	National Schedule of NHS Costs 2021–22, SB11Z: Deliver Exclusively Oral Chemotherapy – Outpatient[185]
Oral drug subsequent	£0.00	Assumption

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

Table 58: Summary of hospitalisation for teclistamab step-up dosing regimen

Step-Up Dosing Regimen Costs	Frequency	Source
Teclistamab hospital days (Week 1)	4	Teclistamab SmPC[139]
Teclistamab hospital days (Week 2)	2	

Abbreviations: SmPC: summary of product characteristics.

Co-Medication

In line with the SmPC for teclistamab and TA510 for PomDex, co-medication was included during step-up dosing on teclistamab and for patients receiving PomDex, as detailed in Table 59.[27, 139]

Pre-medication costs for PomDex including granulocyte colony stimulating factor (G-CSF), red blood cell (RBC) transfusion and platelet transfusion were also included for PomDex in line with TA510, as detailed in Table 60.

The proportion of patients receiving each co-medication (including pre-medication) for teclistamab and PomDex is presented in Table 61.

Table 59: 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	3.13	16.0 mg	Oral subsequent	0.89	BNF 2024
Paracetamol (acetaminophen)	100	500.0 mg	0.60	825.0 mg	Oral subsequent	0.01	BNF 2024
Diphenhydramine	20	25.0 mg	3.87	50.0 mg	Oral subsequent	0.39	MIMS, Nytol
Acetylsalicylic acid	100	75.0 mg	0.46	150.0 mg	Oral subsequent	0.01	eMIT 2023

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

Table 60: Pre-medication procedure costs

Pre-medication	Number doses received	Unit Cost	Source
G-CSF	1.00	59.75	TA510, TA510, cost inflated from 2014/15 to 2021/22 NHSCII P&P Index
RBC Transfusion	3.00	138.15	
Platelet transfusion	4.79	223.31	

Abbreviations: G-CSF: granulocyte-colony stimulating factor; RBC: red blood cell.

Table 61: Proportion of patients receiving each co-medication (including pre-medication) for teclistamab and PomDex

% Patients Receiving Co-Medication	Dexamethasone PO 2 mg	Dexamethasone PO 4 mg	Paracetamol (acetaminophen)	Diphenhydramine	Acetylsalicylic acid	GCSF	RBC transfusion	Platelet transfusion	Source
Tec	100%	0%	100%	100%	0%	0%	0%	0%	Teclistamab SmPC
Pd	0%	0%	0%	0%	33%	43%	49%	20%	TA510/TA783

Abbreviations: G-CSF: granulocyte-colony stimulating factor; RBC: red blood cell; SmPC: summary of product characteristics.

Other costs: Immunoglobin (Ig)

Hypogammaglobulinaemia has been reported in patients receiving teclistamab. [139] In the base case analysis, immunoglobulin (Ig) usage in patients receiving teclistamab is modelled in line with the observed frequency and duration of IV and SC Ig infusions in the MajesTEC-1 trial. A summary of the frequency and duration of Ig in the MajesTEC-1 trial is provided in Table 62.

It is important to note that owing to the international nature of the trial, the eligibility criteria for receiving Ig in the MajesTEC-1 trial were less stringent compared to the criteria currently used in UK clinical practice. The NHS Clinical Commissioning Group requires patients to have hypogammaglobulinemia AND, IgG <4g/L, recurrent or severe bacterial infection and documented vaccine challenge, to be eligible for Ig replacement therapy. [186] Only a portion of the patients receiving Ig in MajesTEC-1 met these specific criteria. Therefore, the estimated usage and associated costs of Ig in the base case analysis are considered to be high estimates. This is supported by the fact that [redacted] and [redacted] of patients in the base case analysis are modelled to receive IV and SC Ig, respectively, based on the observed data from the MajesTEC-1 trial (Table 62). In contrast, when the existing UK restrictions are considered, only [redacted] and [redacted] of patients receiving IVIg and SCIg in the MajesTEC-1 trial would have been eligible for receiving IV or SC Ig, respectively, in UK clinical practice, although the variation for the use of Ig may have potentially impacted safety and efficacy outcomes. The impact of modelling Ig usage in line with UK guidance is explored in a scenario analysis and the pertinent inputs for this scenario can be found in Table 63.

Finally, owing to the national shortages of Ig, an additional scenario analysis was included in the economic model in which Ig utilised was modelled to be zero in patients receiving teclistamab. The results of these additional scenario analysis are presented in Section B.3.11.3.

Drug acquisition costs for Ig treatment were sourced from the BNF (2024) and are summarised in Table 63.[187, 188] 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 much as possible. 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.[186] The administration costs of SC and IV infusion were also taken into consideration in line with the values provided in Table 57.

Table 62: Ig dosing regimen: Base case analysis (Ig usage for any reason)

Method of administration	Mean number of doses	Proportion of patients (%)	Source
IV	[redacted]	[redacted]	MajesTEC-1 (August 23 DCO)[189]
SC	[redacted]	[redacted]	

Abbreviations: Ig: immunoglobulin; IV: intravenous; SC: subcutaneous.

Table 63: Ig dosing regimen: Scenario analysis (restricted to UK guidelines)

Method of administration	Mean number of doses	Proportion of patients (%)	Source
IV	[redacted]	[redacted]	

SC	[redacted]	[redacted]	MajesTEC-1 (August 23 DCO)[105]

Abbreviations: Ig: immunoglobulin; IV: intravenous; SC: subcutaneous.

Table 64: Ig drug acquisition costs

Ig	Units	Strength	Price per pack or unit cost (£)	Dosage per administration
Octagam	1	10.0 g	690.00	29.9 g
Cuvitru	1	10.0 g	570.00	29.9 g

Abbreviations: Ig: immunoglobulin.

B.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 65).

Table 65: 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)	PD	
Haematologist visit	209.41	0.23	0.08	0.08	NICE TA427[163]
Full blood count	2.96	0.21	0.21	0.39	
Biochemistry	7.73	0.19	0.19	0.33	
Average weekly cost by health state (£)		50.25	18.84	20.46	Calculation

Abbreviations: PD: progressed disease; 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 TA897, the end of life cost applied in the model (£13,113.00) was taken from the PSSRU oncology reference costs and accounted for both hospital (£11,407.00) and social care (£1,706.00) in the last year of life.[100]

B.3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving treatment was included in the model. The unit costs per event were based on NHS reference costs 2021–2022 and are presented in Table 66.

Given a national tender in England for tocilizumab will come into effect from March 2024, the impact of an illustrative tender price on the cost of the management of CRS events was explored in a scenario analysis (see Section B.3.11.3). AE unit costs were applied to the proportion of patients experiencing each event in either the teclistamab or PomDex 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 £5,033.00 for teclistamab and £2,830.00 for PomDex, respectively.

Table 66: Summary of AE costs in the base case economic analysis

AE	Unit cost (£)	Source
Anaemia	1,603.06	National Schedule of NHS Costs 2021–22, SA09: Weighted Average of Non-Elective Admissions
Asthenia and fatigue	1,512.86	National Schedule of NHS Costs 2021-22, WH17: Weighted Average of Non-Elective Admissions
CRS, Grade 1–2	1,531.46	Assumed to be the cost of tocilizumab, 8mg/kg for 2 doses based on feedback received from UK clinical

		experts on the management of Grade 1–2 CRS AEs in clinical practice.[83] BNF 2024
CRS, Grade 3+	7,962.02	Assumed to be the cost of tocilizumab, 8mg/kg for 2 doses, plus 3 days ICU based on feedback received from UK clinical experts on the management of Grade 3+ CRS AEs in clinical practice.[83]
Dyspnoea	539.17	National Schedule of NHS Costs 2021-22, DZ19L, DZ19M, DZ19N: Weighted average of Day Case (Per TA567 [2018]
Febrile neutropenia	2,335.50	National Schedule of NHS Costs 2021–22, SA35: Weighted Average of Non-Elective Admissions
Hypertension	781.13	National Schedule of NHS Costs 2021-22, EB04Z: Weighted Average of Non-Elective Admissions
Hypophosphatemia	1,831.57	Assumed equal to hypokalaemia, as per TA658
Leukopenia	1,772.97	National Schedule of NHS Costs 2021/22, SA08: Weighted Average of Non-Elective Admissions
Lymphopenia	1,772.97	National Schedule of NHS Costs 2021/22, SA08: Weighted Average of Non-Elective Admissions
Neurotoxicity, Grade 1–2	0.00	Assumed to be captured within the hospitalisation cost of CRS (Grade 1–2)
Neurotoxicity, Grade 3+	0.00	Assumed to be captured within the hospitalisation cost of CRS (Grade 3+)
Neutropenia	2,335.50	National Schedule of NHS Costs 2021-22, SA35: Weighted Average of Non-Elective Admissions
Pneumonia	1,273.81	National Schedule of NHS Costs 2021-22, CB02: Weighted Average of Non-Elective Admissions
Thrombocytopenia	2,163.16	National Schedule of NHS Costs 2021-22, SA12: Weighted Average of Non-Elective Admissions

Abbreviations: AE: adverse event; CRS: cytokine release syndrome; NHS: National Health Service.

B.3.5.4 Subsequent treatments

Distribution of subsequent treatments

Table 67 presents a summary of the top 10 subsequent treatment regimens administered to patients in the MajesTEC-1 study and the ECOG 0-1 PomDex subpopulation of the UK RW TCE cohort study (N=645).

Table 67: Summary of subsequent treatments in MajesTEC-1 and the UK RW TCE cohort study

MajesTEC-1 (n=165)		UK RW TCE PomDex ECOG 0-1 subgroup (n=645)[a]	
Subsequent treatment	**Proportion[b]**	**Subsequent treatment**	**Proportion**
Talquetamab	[redacted]	Bortezomib panobinostat	62.2%
Carfilzomib-Dexamethasone	[redacted]	Melphalan thalidomide	11.7%
Cyclophosphamide-Dexamethasone-Pomalidomide	[redacted]	Cyclophosphamide thalidomide	8.9%

Belantamab Mafodotin	[redacted]	Melphalan	5.6%
Bortezomib-Cyclophosphamide-Dexamethasone	[redacted]	Cyclophosphamide	5.0%
Dexamethasone	[redacted]	Cyclophosphamide pomalidomide	5.0%
Bendamustine	[redacted]	Bendamustine thalidomide	3.3%
Bortezomib-Dexamethasone	[redacted]	Bortezomib	2.8%
Carfilzomib-Cyclophosphamide-Dexamethasone	[redacted]	Bendamustine	2.2%
Dexamethasone-Isatuximab-Pomalidomide	[redacted]	Bortezomib melphalan	1.7%

Footnote: [a]Dexamethasone use was not recorded in the UK RW TCE study. [b]Percentages were calculated based on the number of patients who received subsequent therapies in each arm (n=64 for MajesTEC-1 and n=180 for PomDex)
Abbreviations: CAR-T: chimeric antigen receptor T-cells; NCRAS: National Cancer Registration and Analysis Service; PomDex: pomalidomide in combination with dexamethasone; RWE: real-world evidence.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO); Janssen. Data on File. UK NCRAS study (October 2023 DCO).[24, 105]

As a simplifying assumption, only subsequent treatments received by ≥2% patients in either the MajesTEC-1 or UK RW TCE cohort study were included as subsequent treatments for teclistamab and PomDex, respectively in the economic model. In both MajesTEC-1 and the UK RW TCE cohort study, there were instances of patients receiving subsequent treatment regimens which are not routinely available in UK clinical practice.

In order to ensure subsequent treatment costs were reflective of the UK treatment pathway, the subsequent treatment distributions in both studies were re-weighted to remove subsequent treatments not routinely available in the UK. This re-weighting was applied to derive subsequent treatment costs only; as discussed in Section B.3.3.2, the teclistamab OS data in MajesTEC-1 were adjusted separately to remove the effects of subsequent treatments on OS.

The resulting re-weighted subsequent treatment distributions used to inform the costs of subsequent treatments following teclistamab and PomDex in the economic model are presented in Table 68. A scenario analysis was conducted where the subsequent treatments following teclistamab are also informed by the UK RWE TCE study distribution, as detailed in Table 68.

A summary of the modelled dosing regimens and associated costs for each subsequent therapy regimen can be found in Appendix K.

Table 68: Summary of subsequent treatment distributions (re-weighted) following either teclistamab or PomDex in the base case analysis

Treatment	Teclistamab (MajesTEC-1)	Treatment	PomDex (UK RW TCE)[a]
Cyclophosphamide + Pomalidomide + Dexamethasone	[redacted]	Bortezomib + Panobinostat + dexamethasone	58.3%

Dexamethasone	[redacted]	Melphalan + Thalidomide	10.9%
Melphalan + Dexamethasone	[redacted]	Cyclophosphamide + Thalidomide	8.3%
Bortezomib + Cyclophosphamide + Dexamethasone	[redacted]	Melphalan	5.2%
Cyclophosphamide + Dexamethasone	[redacted]	Cyclophosphamide + dexamethasone	4.7%
Bendamustine	[redacted]	Cyclophosphamide + pomalidomide + dexamethasone	4.7%
Bortezomib + Dexamethasone	[redacted]	Bendamustine + thalidomide	3.1%
Bendamustine + Prednisolone	[redacted]	Bortezomib + dexamethasone	2.6%
CEDP	[redacted]	Bendamustine	2.1%
Pomalidomide + Dexamethasone	[redacted]		

[a]Dexamethasone use was not recorded in the UK RW TCE cohort study. To more accurately reflect UK clinical practice, treatment regimens that would commonly include dexamethasone were modelled to include dexamethasone, including: cyclophosphamide; melphalan; bortezomib; cyclophosphamide and pomalidomide; bortezomib and cyclophosphamide; bortezomib and panobinostat.
Abbreviations: PomDex: pomalidomide in combination with dexamethasone.
Source: Janssen. Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO); Janssen. Data on File. UK NCRAS study (October 2023 DCO).[24, 105]

Proportion of patients on subsequent treatment and duration of treatment

Real-world attrition rates between lines of subsequent therapy are high in MM and is well characterised in the literature.[152, 190, 191] As such, in both treatment arms, it was assumed that 52.6% of patients go on to receive a subsequent treatment following disease progression on teclistamab or PomDex based on Djebbari et al. (2020)[153], a real-world study of UK MM patients. This approach is consistent with the approach used in NICE TA889 (cilta-cel appraisal) and NICE TA658 (IsaPomDex appraisal).

Patients were assumed to receive a median of 4 months of subsequent treatment in both arms, based on Yong et al. (2016).[35] This assumption was validated by UK clinical experts and in line with the Committee's preferred assumptions in NICE TA889.{, #282}

Two scenario analyses were conducted to explore these assumptions further in Section B.3.11.3. The first scenario analysis involved modifying the proportion of patients receiving subsequent therapies in the teclistamab arm to [redacted]%, informed by data collected during the MajesTEC-1 trial. This proportion aligns with the proportion of patients in MajesTEC-1 who received subsequent treatment following disease progression. The second scenario analysis assumed distinct duration of subsequent therapies for each arm, with a shorter duration of subsequent treatment following PomDex (2 months) compared to teclistamab (4 months).

B.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.[192] The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[193] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2018–2020.[194] 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.[195] The baseline characteristics for the modelled population was informed by the PomDex cohort in the UK RW TCE cohort study as these are most representative of the population in UK clinical practice (Section B.2.9.1). The total QALYs for the current MM population in the UK were based on the results of the base case economic analysis for PomDex (i.e. using utility values for PF and PD from the PomDex base case approach), as shown in Table 69.

As shown in Table 70, the results of the severity modifier calculations demonstrate that teclistamab is eligible for a 1.2x severity modifier when compared to PomDex, based on a proportional QALY shortfall of [redacted], highlighting the poor prognosis faced by patients with TCE RRMM on current treatment.

Table 69: 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 B.3.2.1
Proportion of female patients (%)	[redacted]	Section B.3.2.1
Health state utility: PF	0.61[38]	Section B.3.4.5
Health state utility: PD	0.57[38]	Section B.3.4.5

Abbreviations: PD: progressed disease; PF: progression-free; QALY: quality-adjusted life year

Table 70: 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]	1.2

Abbreviations: QALY: quality-adjusted life year.

B.3.7 *Uncertainty*

Despite a thorough ITC approach, with the commissioning of the UK RW TCE cohort study to source IPD data for PomDex, the ITC is not able to adjust for all prognostic variables in imbalance between study populations

Since the MajesTEC-1 trial was a single-arm study, comparative efficacy estimates for teclistamab versus PomDex needed to be generated through indirect treatment comparison. In the base case economic analysis, comparative effectiveness was derived from the IPTW ITC previously detailed in Section B.2.9. While there may be residual uncertainties in the ITC that could potentially influence the economic model, the ITC should be recognised as the most robust approach available given the existing data for PomDex. Notably, the use of a UK-specific dataset for PomDex that directly reflects patients with TCE RRMM represents a significant strength of the economic analysis. It is also important to emphasise that the ITC results were highly consistent across all sensitivity analyses conducted, and that the base case ITC analysis yielded the most conservative results among all the sensitivity analyses, including the naïve (unadjusted) comparison. Together, this body of evidence strongly supports the statistically significant and clinically meaningful benefits of teclistamab compared to PomDex.

Long-term uncertainty remains despite the use of the [redacted] DCO from MajesTEC-1

Long-term extrapolation of the PFS and OS data from the MajesTEC-1 trial were required, which is inevitably associated with uncertainty. However, this uncertainty was mitigated by the relatively mature survival data obtained from the [redacted] data-cut off of MajesTEC-1, with median OS reached and 57% of OS events already observed.

Additionally, elicited expectations from extensive consultations with UK-based clinical experts, as part of this appraisal, were incorporated to inform the modelled long-term extrapolations of survival for patients with triple-class exposed RRMM treated with either teclistamab or PomDex.

The selection of the teclistamab base case extrapolations for OS and PFS underwent a rigorous process which applied an attenuation effect to calibrate the long-term survival estimates with expert estimates while also maintaining the statistically best fit to the observed data. Together, this approach ensured that the chosen extrapolation had both high internal and external validity.

B.3.8 *Managed access proposal*

This submission [redacted] a proposal for managed access - the teclistamab data in this submission are based on [redacted], and [redacted] data are expected to become available in this patient population to inform decision making.

B.3.9 *Summary of the base-case analysis inputs and assumptions*

B.3.9.1 Summary of base case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 71.

Table 71: 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 B.3.2.2
Time horizon	Lifetime (40 years)				
Patient baseline characteristics					
Mean age, years	[redacted]				Section B.3.2.1
Proportion of female patients (%)	[redacted]				
Mean body weight, kg	[redacted]				
Mean BSA, m^2	[redacted]				
Survival inputs					
	PFS	**OS**	**TTD**	**QW/Q2W Dose Switching**	Section B.3.3.2−B.3.3.5
Teclistamab	Calibrated Log-Normal	Calibrated Log-Normal	Gamma	Gompertz	
PomDex	Gompertz	Gompertz	HR (between PFS and TTD for teclistamab) applied to PomDex PFS	N/A	
AEs					
	Teclistamab		**PomDex**		Section B.3.3.7
Anaemia	37.6%		32.7%		
Asthenia and fatigue	[redacted]		9.0%		
CRS, Grade 1–2	71.5%		0.0%		
CRS, Grade 3+	0.6%		0.0%		
Dyspnoea	0.0%		5.0%		
Febrile neutropenia	[redacted]		9.3%		
Hypertension	[redacted]		0.0%		
Hypophosphatemia	[redacted]		0.0%		
Leukopenia	9.1%		9.0%		
Lymphopenia	34.5%		0.0%		

Neurotoxicity, Grade 1-2	[redacted]	0.0%	
Neurotoxicity, Grade 3+	[redacted]	0.0%	
Neutropenia	65.5%	48.3%	
Pneumonia	[redacted]	12.7%	
Thrombocytopenia	23.0%	22.0%	
Utility inputs			
PF (SD)	Time-dependent – see Table 52	0.610 (0.010)	Section B.3.4.5
PD (SD)	[redacted] ([redacted])	0.570 (0.010)	
Adverse event disutility			
	Utility decrement	**Duration of AE**	Section B.3.4.4
Anaemia	-0.3100	[redacted]	
Asthenia and fatigue	-0.1150	[redacted]	
CRS, Grade 1–2	-0.1109	[redacted]	
CRS, Grade 3+	[redacted]	[redacted]	
Dyspnoea	-0.0500	[redacted]	
Febrile neutropenia	-0.3900	[redacted]	
Hypertension	0.0000	[redacted]	
Hypophosphatemia	-0.1500	[redacted]	
Leukopenia	-0.0650	[redacted]	
Lymphopenia	-0.0650	[redacted]	
Neurotoxicity, Grade 1–2	0.0000	[redacted]	
Neurotoxicity, Grade 3+	0.0000	[redacted]	
Neutropenia	-0.1450	[redacted]	
Pneumonia	-0.1900	[redacted]	
Thrombocytopenia	-0.3100	[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			
Acquisition cost: teclistamab 30 mg/3 ml solution for injection	List price: £775.14 PAS price: [redacted]		Section B.3.5.1
Acquisition cost: teclistamab 153	List price: £3,952.78 PAS price: [redacted]		

mg/1.7 ml solution for injection			
Acquisition cost: pomalidomide 4 mg	£8,884.00		
Acquisition cost: dexamethasone 2.0 mg	£3.27		
Co-medication and pre-medication procedure costs			
Co-medication	**Cost per admin**		Section B.3.5.1
Dexamethasone PO 2 mg	£0.89		
Paracetamol (acetaminophen)	£0.01		
Diphenhydramine	£0.39		
Acetylsalicylic acid	£0.01		
Pre-medication	**Unit cost**		
G-CSF	£59.75		
RBC Transfusion	£138.15		
Platelet transfusion	£223.31		
Co-medication and pre-medication usage	**PomDex**	**Teclistamab**	
Dexamethasone PO 2 mg	100%	0%	Section B.3.5.1
Paracetamol (acetaminophen)	0%	0%	
Diphenhydramine	100%	0%	
Acetylsalicylic acid	100%	0%	
G-CSF	0%	33%	
RBC Transfusion	0%	43%	
Platelet transfusion	0%	49%	
Ig usage for Teclistamab	**Mean number of doses**	**Proportion of patients**	
IV Ig	[redacted]	[redacted]	Section B.3.5.1
SC Ig	[redacted]	[redacted]	
Ig Costs	**Unit costs**		
IV Ig (Octagram)	690.00	N/A	
SC Ig (Cuvitru)	570.00	N/A	
Administration costs (per admin)			
Complex first IV infusion	£485.23		Section B.3.5.1
Other IV administration	£326.46		
Each SC administration	£119.00		

Oral drug initiation	£197.25			
Oral drug subsequent	£0.00			
Monitoring costs				
Haematologist visit	£209.41			Section B.3.5.2
Full blood count	£2.96			
Biochemistry	£7.73			
End of life costs	£13,113.00			
AE costs				
Anaemia	£1,603.06			Section B.3.5.3
Asthenia and fatigue	£1,512.86			
CRS, Grade 1–2	£1,531.46			
CRS, Grade 3+	£7,962.02			
Dyspnoea	£539.17			
Febrile neutropenia	£2,335.50			
Hypertension	£781.13			
Hypophosphatemia	£1,831.57			
Leukopenia	£1,772.97			
Lymphopenia	£1,772.97			
Neurotoxicity, Grade 1–2	£0.00			
Neurotoxicity, Grade 3+	£0.00			
Neutropenia	£2,335.50			
Pneumonia	£1,273.81			
Thrombocytopenia	£2,163.16			
Subsequent treatment distribution				
Treatment	**Teclistamab**	**PomDex**	**Proportions**	
Cyclophosphamide + Pomalidomide + Dexamethasone	[redacted]	Bortezomib + Panobinostat + dexamethasone	58.3%	Section B.3.13
Dexamethasone	[redacted]	Melphalan + Thalidomide	10.9%	
Melphalan + Dexamethasone	[redacted]	Cyclophosphamide + Thalidomide	8.3%	
Bortezomib + Cyclophosphamide + Dexamethasone	[redacted]	Melphalan	5.2%	
Cyclophosphamide + Dexamethasone	[redacted]	Cyclophosphamide + dexamethasone	4.7%	
Bendamustine	[redacted]	Cyclophosphamide + pomalidomide + dexamethasone	4.7%	

Bortezomib + Dexamethasone	[redacted]	Bendamustine + thalidomide	3.1%	
Bendamustine + Prednisolone	[redacted]	Bortezomib + dexamethasone	2.6%	
CEDP	[redacted]	Bendamustine	2.1%	
Pomalidomide + Dexamethasone	[redacted]			

Abbreviations: BSA: body surface areas; CRS: cytokine release syndrome; HR: hazard ratio; IV; intravenous; N/A: not applicable; QW/Q2W: once weekly/ bi-weekly; PD: progressed disease; PFS: progression-free survival; SC: subcutaneous; SD: standard deviation; TTD: time to treatment discontinuation; OS: overall survival.

B.3.9.2 Assumptions

A summary of the assumptions utilized in the base case economic analysis can be found in Table 72.

Table 72: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Clinical Effectiveness		
PFS (TTNT)	TTNT is assumed to be equal to PFS	As previously detailed in Section B.2.6.6, PFS were unavailable for PomDex. As TTNT and PFS data observed in MajesTEC-1 were highly consistent, the use of TTNT as a proxy for PFS does not represent a source of uncertainty
Survival models		
OS curves	Teclistamab OS is modelled by independent extrapolation of the adjusted OS data from the MajesTEC-1 trial using the log-normal curve. The log-normal curve was additionally calibrated to long-term survival estimates of 10% and 3% at 10 and 15 years, respectively, in line with UK clinical expert estimates. PomDex OS is modelled by independent extrapolation of the OS data from the UK RW TCE cohort study using the Gompertz curve	The results of the proportional hazard assessment found that the proportional hazard assumption did not hold for OS. As such, it was considered more appropriate to independently extrapolate OS for teclistamab and PomDex in the base case economic analysis – particularly given the fundamental differences in mechanism of actions between the two treatments. The log-normal curve was associated with the best statistical fit to the adjusted OS data from MajesTEC-1 (and therefore the highest internal validity), reflected the smoothed hazard profile of OS in MajesTEC-1, and also aligned with the UK clinical expert estimates of survival at 5 years. None of the extrapolations provided both high internal and external validity. The lognormal was therefore calibrated after 5-years to bring the long-term survival estimates in line with the midpoint of the range of clinically plausible estimates provided by UK clinical experts. Additional adjustment was also made to the teclistamab OS KM data, whereby the survival time was reduced for patients initiating a subsequent treatment which is not available in routine UK clinical practice in line with the simplified two-stage approach outlined in NICE TSD 16.[175]

		Overall, these approaches enabled the generation of an OS extrapolation for teclistamab with both high internal and external validity, which could not be provided by any of the standard parametric extrapolations. The selection of extrapolation for OS for PomDex was based on statistical fit, visual inspection and long-term clinical plausibility, based on feedback from UK clinical experts collected as part of this appraisal.
PFS curves	Teclistamab PFS is modelled by independent extrapolation of the adjusted TTNT data (proxy for PFS) from the MajesTEC-1 trial using the log-normal curve. The log-normal curve was additionally calibrated after 5-years to long-term PFS estimates of 5% and 1% at 10 and 15 years, respectively, in line with UK clinical expert estimates. PomDex PFS is modelled by independent extrapolation of the TTNT data from the UK RWE TCE study using the Gompertz curve	Similarly to OS, the results of the proportional hazard assessment found that the proportional hazard assumption did not hold, and PFS was independently extrapolated between PomDex and teclistamab. The log-normal extrapolation was associated with the best statistical fit to the TTNT [proxy for PFS] data from the ATC-adjusted MajesTEC-1 data (and therefore, the highest internal validity), and also aligned with the UK clinical expert estimates of PFS at 5 years., The lognormal was therefore calibrated after 5 years to bring the long-term survival estimates in line with the midpoint of the range of clinically plausible estimates provided by UK clinical experts, allowing the generation of a PFS extrapolation for teclistamab with both high internal and external validity, which could not be provided by any of the standard parametric extrapolations. The selection of extrapolation for TTNT [proxy for PFS] for PomDex was based on statistical fit, visual inspection and long-term clinical plausibility, based on feedback from UK clinical experts collected as part of this appraisal.
TTD	Teclistamab TTD is modelled by independent extrapolation of the TTD data from the MajesTEC-1 trial using the Gamma curve. In the absence of TTD data from PomDex, the relationship between PFS and TTD for teclistamab was assumed to be the same for PomDex. TTD for	The selection of the TTD extrapolation for teclistamab was based on statistical fit, visual inspection and long-term clinical plausibility, based on the feedback from UK clinical experts collected as part of this appraisal – once the clinically implausible curves were ruled out, the Gamma was chosen as the midpoint of the three similar remaining curves.

	PomDex was therefore derived by applying a HR (derived from the relative difference between PFS [using TTNT as a proxy] and TTD for teclistamab) to the chosen PFS extrapolation for PomDex	In the absence of TTD data for PomDex from the UK RW TCE cohort study, the next best option was to assume that the same relationship between PFS and TTD for teclistamab, as observed in MajesTEC-1, held for PomDex.
Costs		
Drug wastage	Drug wastage was assumed to be 15%	Aligned with the accepted approach in the NICE appraisal for belantamab mafodotin (ID2701).[22] Furthermore, UK clinical experts consulted during validation interviews as part of this submission highlighted that vial sharing is maximised in clinical practice and therefore an assumption of 15% drug wastage is likely an overestimate, meaning this assumption is reasonable.
Dose switching	A dose switching curve has been utilised to estimate the proportion of patients switching to Q2W dosing over time. The remaining patients were assumed to remain on a weekly dosing regimen	Assuming that a proportion of patients switch to a biweekly dosing regimen is aligned with the observed data from the MajesTEC-1 trial as well as the licensed dosing regimen for teclistamab.
Proportion of patients receiving subsequent treatment	It is assumed that 52.6% of patients who experience disease progression go onto receive subsequent treatment	This estimate of 52.6% of patients receiving subsequent treatment is based on a recent UK study by Djebbari et al. (2020)[153], and was considered to be an appropriate assumption by UK clinical experts
Subsequent treatments	Following either teclistamab or PomDex, patients receive subsequent therapy for a mean duration of 4 months.	In the absence of data on the duration of subsequent treatments from either the MajesTEC-1 or UK RW TCE cohort studies, an estimated mean duration of four months for this line of multiple myeloma treatment was derived from Yong et al. (2016).[35] This value was validated as appropriate by UK clinical experts consulted as part of an Advisory Board meeting in December 2023
Ig costs	In the base case analysis, Ig costs were modelled in line with the usage of IV and SC Ig observed in the MajesTEC-1 trial	In the absence of available data on 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.[186] 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 [redacted] and [redacted] 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 [redacted] and [redacted] 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. The impact on the economic results of modelling Ig usage in line with UK requirements is explored in a scenario analysis (see Section B.3.11.3)
Utility values		
Treatment dependent HSUVs	In the base case analysis HSUVs were modelled to be treatment dependent	Treatment dependent HSUVs were considered appropriate given that multiple studies have shown that MM treatments which drive a deeper response are associated with improvements in patient HRQoL; an SLR conducted in 2022 to identify data on the relationship between HRQoL and clinical response in MM patients found that almost all studies (12/14) reported that deeper responses resulted in improved patient HRQoL. [84] This observation is intuitive given patients achieving deeper quality of response have a reduced number of myeloma cells which are able to cause ongoing bone damage, thereby resulting in reduced symptoms and therefore intuitive improvements in HRQoL. In this respect, as detailed in Section B.2.6.1, 59.4% of patients receiving teclistamab achieved a VGPR or better in MajesTEC-1 (including 38.8% of patients achieving an sCR), compared with 7% of patients who achieved a VGPR or better in the MM-003 trial – a striking greater than 7 fold increase in the VGPR rate for teclistamab

		versus PomDex. As such, considering the correlation between depth of response and patient HRQoL, use of treatment dependent HSUVs is considered appropriate.
Time dependent utilities for PFS for teclistamab	In the base case analysis utility values for teclistamab were assumed to be time dependent in the progression-free health state	EQ-5D data collected during MajesTEC-1 demonstrated that patients utility values improved with increasing time spent in the progression-free health state and therefore use of time dependent utilities was considered appropriate for the teclistamab arm. Furthermore, feedback received from UK clinical experts in MM noted that time-dependent utility values were more appropriate given that an initial dip in quality of life is typically observed in patients initiating treatment whilst they receive step-up dosing, correlating to active disease, which then improves with increased time spent progression-free.[83] As there are no data to suggest that utilities vary over time for patients treated with PomDex, the HSUV for PF was modelled to be time-independent in the base case analysis. The variations in utility over-time observed in the MajesTEC-1 trial are likely to be associated with the deepening of responses over time; as previously detailed in Section B.2.6.3, the mean time to first response to teclistamab is [redacted] months, with a mean time and a mean time to CR or better of [redacted] months. In contrast, only a very small proportion of patients receiving PomDex are likely to ever achieve CR, meaning that a similar deepening of responses and subsequent improvement in HRQoL over time is unlikely and therefore time-dependent utilities for the PF health state are unlikely to be appropriate.
Grade ≥3 CRS disutility	Grade ≥3 CRS disutility amounts to death (utility score of 0) for duration of the event	Consistent with previous CAR-T appraisals in the USA[196] and the UK,[197, 198] including the York report on the assessment of regenerative medicines and cell therapy products.[198]

Abbreviations: CRS: cytokine release syndrome; HR: hazard ratio; NCRAS: National Cancer Registration Analysis Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; SmPC: Summary of Product Characteristics; TTD: time to treatment discontinuation; TSD: Technical Support Document; TTNT: time to next treatment.

B.3.10 *Base-case results*

Results of the economic analysis are presented in Section B.3.10 below.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for teclistamab (list price) versus PomDex (list price) are presented in Table 73 and Table 75, respectively. The base case deterministic and probabilistic cost-effectiveness results for teclistamab (with-PAS) versus PomDex are presented in Table 77 and Table 79, respectively. Janssen acknowledges that a confidential simple PAS discount is available for PomDex. However, as this price is not available, it was excluded from ICER calculations.

At PAS price, teclistamab was found to be a cost-effective use of NHS resources when compared to PomDex at a WTP threshold of £30,000/QALY in both the deterministic and probabilistic analyses. Additionally, in both the deterministic and probabilistic analyses teclistamab was found to be [redacted] versus PomDex regardless of whether a severity modifier was applied (Table 78–and Table 80).

In all base case analyses, teclistamab was associated with positive incremental LYGs ([redacted]) and QALYs (ranging from and [redacted]) versus PomDex. The positive incremental QALYs increased to [redacted] once the 1.2x severity modifier was applied. These results highlight the improvements in both quality and length of life that teclistamab may offer to patients in this setting who have otherwise reached the end of the treatment pathway.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 73: Deterministic base-case results (TEC list price, no severity modifier)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Teclistamab	£201,341	[redacted]	[redacted]	-	-	-	-	-
PomDex	£109,342	[redacted]	[redacted]	£91,999	[redacted]	[redacted]	£67,217	-1.70

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 74: Deterministic base-case results (TEC list price, 1.2x severity modifier)

Intervention	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab vs PomDex	£91,999	[redacted]	[redacted]	£56,014	-1.42

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 75: Probabilistic base-case results (TEC list price, no severity modifier)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab	£199,356	[redacted]	[redacted]	-	-	-	-	-
PomDex	£107,335	[redacted]	[redacted]	£92,021	[redacted]	[redacted]	£68,342	-1.72

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 76: Probabilistic base-case results (TEC list price, 1.2x severity modifier)

Intervention	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab vs PomDex	£92,021	[redacted]	[redacted]	£56,952	-1.45

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 77: Deterministic base-case results (TEC PAS price, no severity modifier)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB at £30,000
Teclistamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-
PomDex	£109,342	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 78: Deterministic base-case results (TEC PAS price, 1.2x severity modifier)

Intervention	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab vs PomDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 79: Probabilistic base-case results (TEC PAS price, no severity modifier)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab	[redacted]	[redacted]	[redacted]	-	-	-	-	-
PomDex	£107,335	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 80: Probabilistic base-case results (TEC PAS price, 1.2x severity modifier)

Intervention	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	Incremental NHB
Teclistamab vs PomDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

B.3.11 *Exploring uncertainty*

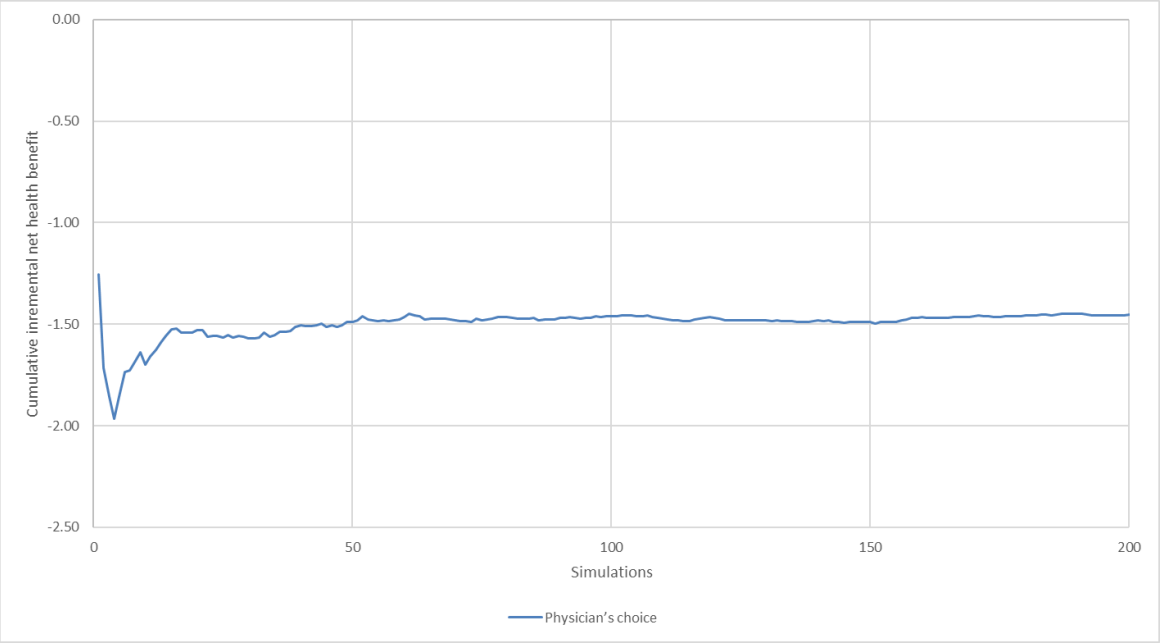
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section B.3.11.3. 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.

B.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 200 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 and list price of teclistamab in Figure 50 and Figure 51 below and demonstrate that the cumulative INHB stabilised after approximately 100 iterations.

Figure 50: INHB convergence plot (TEC list price, no severity modifier)



Abbreviations: INHB: incremental net health benefit; TEC: teclistamab.

Figure 51: INHB convergence plot (TEC PAS price, no severity modifier)

Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme; TEC: teclistamab.

The probabilistic cost-effectiveness planes for teclistamab versus PomDex are presented Figure 52 (list price) and Figure 53 (with-PAS). The figures demonstrates that the cost-effectiveness conclusions of the base case analysis are robust to uncertainty surrounding the model inputs, with teclistamab remaining [redacted] versus PomDex in every iteration, when considering the with-PAS price of teclistamab. The cost-effectiveness acceptability plots are presented in Figure 54 and Figure 55; at the with-PAS price, the PSA found the probability of teclistamab 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.

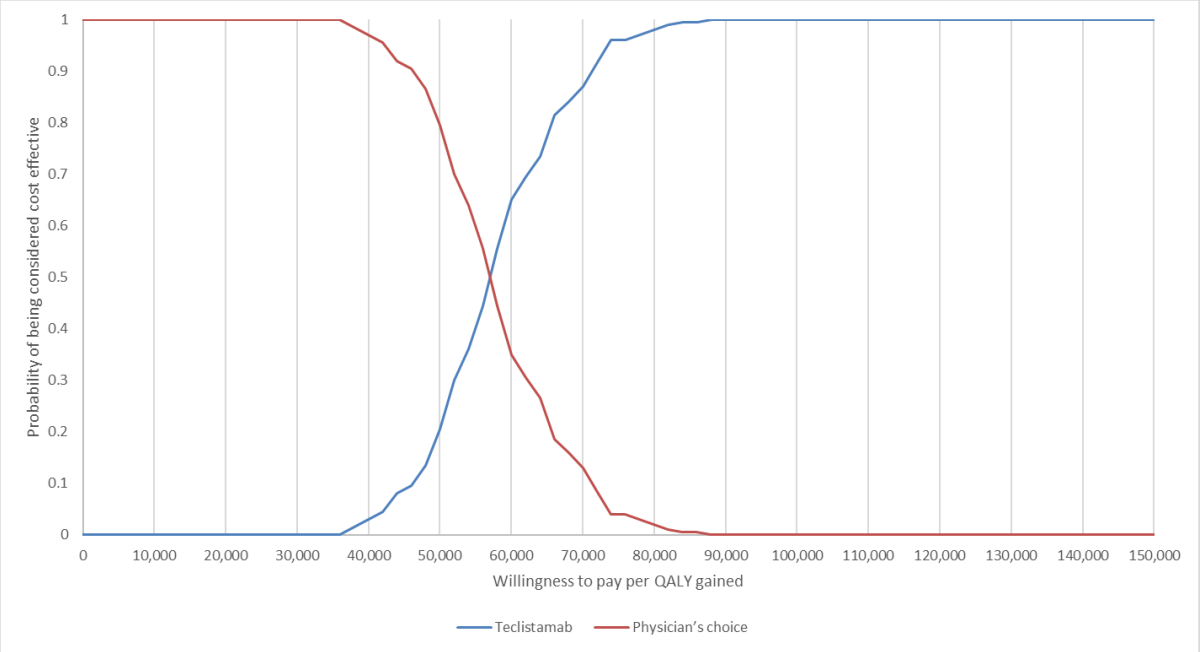
Figure 52: Probabilistic cost-effectiveness plane for TEC vs PomDex (TEC list price, no severity modifier)

Abbreviations: QALYs: quality adjusted life years; TEC: teclistamab; WTP: willingness-to-pay threshold.

Figure 53: Probabilistic cost-effectiveness plane for TEC vs PomDex (TEC PAS price, no severity modifier)

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; TEC: teclistamab; WTP: willingness-to-pay threshold.

Figure 54: Cost-effectiveness acceptability curve for TEC vs PomDex (TEC list price, no severity modifier)



Abbreviations: QALYs: quality adjusted life years; TEC: teclistamab; WTP: willingness-to-pay threshold.

Figure 55: Cost-effectiveness acceptability curve for TEC vs PomDex (TEC PAS price, no severity modifier)

[redacted]

Abbreviations: PAS: patient access scheme; QALYs: quality adjusted life years; TEC: teclistamab; WTP: willingness-to-pay threshold.

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, DSAs were 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%.

Tornado diagrams showing the top 10 most influential parameters on the incremental net health benefit (INHB) for teclistamab versus PomDex at list price is presented in Figure 56 and for teclistamab (with-PAS) versus PomDex in Figure 57. None of the inputs were found to significantly impact the INHB when varied to their limits, with no changes to the base case cost-effectiveness conclusions observed. The INHB was found to be most sensitive to the mean body weight of patients, the final time-dependent utility value for the PF state and the PD HSUV; these are discussed sequentially below.

Mean body weight

The mean body weight utilised in the economic model was based on the mean body weight of patients enrolled in the MajesTEC-1 trial, adjusted to align with patient population of the UK RW TCE cohort study (see Section B.2.9.1). As this cohort study represents a real-world evidence study in UK TCE RRMM patients and therefore is conducted in the exact patient population that is anticipated to receive teclistamab in UK clinical practice, the mean body weight used in the economic model is considered appropriate for decision-making.

HSUVs

Given that the final time-dependent utility value used in the PFS health state for patients receiving teclistamab was held for the remainder of time patients spent in the PFS health state (see Section B.3.4.5) it is not unsurprising that this value was one of the most influential parameters in the model. As highlighted in Section B.3.4.5, the utility values utilised in the base case analysis were informed by feedback received from UK clinical experts in MM and therefore are deemed the most appropriate for decision-making.[176] Uncertainty surrounding the choice of base case HSUVs was however explored in a scenario analysis, the results of which are provided in Section B.3.11.3. Finally, the PD HSUV utilised in the base case analysis for teclistamab was derived directly from the MajesTEC-1 trial data and validated by UK clinical experts as appropriate.[176] As such, the value used in the base case analysis is considered the most relevant for decision-making.

Figure 56: DSA tornado diagram for TEC vs PomDex, INHB (TEC list price, no severity modifier)

Abbreviations: INHB: incremental net health benefit; Pd: pomalidomide + dexamethasone; PFS: progression-free survival; PPS: post-progression survival SC: subcutaneous; TEC: teclistamab.

Figure 57: DSA tornado diagram for TEC vs PomDex, INHB (TEC PAS price, no severity modifier)

Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme; Pd: pomalidomide + dexamethasone; PFS: progression-free survival; PPS: post-progression survival SC: subcutaneous; TEC: teclistamab.

B.3.11.3 Scenario analysis

As described in Section B.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 81.

The INHB was found to be most sensitive to the HSUVs used to inform the PF and PD health states and the calibration applied to the OS extrapolation for teclistamab, with a maximum variation of ± [redacted] from the base case analysis observed.

None of the scenario analyses changed the cost-effectiveness conclusions of the base case analysis; teclistamab remained [redacted] versus PomDex in all analyses and the changes in IHNB were minor, demonstrating that the base case results are associated with minimal uncertainty.

In conclusion, the results of the scenario analyses demonstrate that the results of the base case analysis are robust to uncertainties in the model inputs and assumptions.

Table 81: Summary of scenario analyses

Scenario	Description of Scenario Analysis	Rationale
1a: Teclistamab PFS	Teclistamab PFS: Informed by INV-PFS	In the base case, TTNT data from MajesTEC-1 are used as a proxy for teclistamab PFS, to align with the use of TTNT to inform PFS for PomDex based on the UK RW TCE cohort study. For the reasons previously detailed in Section B.2.9, this assumption is not considered to represent a major source of uncertainty, but this scenario explores the use of investigator-assessed PFS data from MajesTEC-1, weighted to match the UK RW TCE cohort study, rather than TTNT.
1b: Teclistamab PFS	Teclistamab PFS: Informed by IRC-assessed PFS	This scenario explores the use of IRC PFS data from MajesTEC-1, weighted to match the UK RW TCE cohort study cohort, rather than TTNT.
2a: Teclistamab PFS	Teclistamab PFS Attenuation: Adjusted to match the upper limit of the clinical expert estimates of survival (8% at 10 years, 2% at 15 years)	This optimistic scenario uses the upper limits of the clinical expert estimates, adjusting the PFS extrapolation to result in 10-year PFS of 8% and 15-year PFS of 2%.
2b: Teclistamab PFS	Teclistamab PFS Attenuation: Adjusted to match the lower limit of the clinical expert estimates of survival (2% at 10 years, 0% at 15 years)	This pessimistic scenario uses the lower limits of the clinical expert estimates, adjusting the PFS extrapolation to result in 10-year PFS of 2% and 15-year PFS of 0%.
3: PomDex PFS	PomDex PFS: Exponential	Of the two best statistically fitting curves, the Gompertz extrapolation was preferred in the base case to the exponential as it was more closely aligned with UK clinical expert estimates of PFS. The use of the exponential is explored in this scenario analysis.

4a: Teclistamab OS extrapolation	Teclistamab OS attenuation: calibrated to match the upper limit of the clinical expert estimates of survival (15% at 10 years, 5% at 15 years)	This optimistic scenario uses the upper limits of the clinical expert estimates, adjusting the PFS extrapolation to result in 10-year OS of 15% and 15-year OS of 5%.
4b: Teclistamab OS Extrapolation	Teclistamab OS Attenuation: calibrated to match the lower limit of the clinical expert estimates of survival (5% at 10 years, 1% at 15 years)	This pessimistic scenario uses the lower limits of the clinical expert estimates, adjusting the PFS extrapolation to result in 10-year OS of 5% and 15-year OS of 1%.
5: PomDex OS extrapolation	PomDex OS Extrapolation: Exponential	In the base case, the Gompertz extrapolation was preferred to the exponential due to being more closely aligned with the UK clinical expert estimates of OS out of the two best statistically fitting curves. The exponential extrapolation was explored in this scenario analysis.
6: Teclistamab TTD	Teclistamab TTD: Weibull	In the base case, the Gamma extrapolation was chosen to model teclistamab TTD, as the midpoint of the three remaining extrapolations once the clinically implausible extrapolations were excluded. The Weibull extrapolation was considered in this scenario analysis.
7a: Health state utility values	PomDex and teclistamab HSUVs are informed by the time-dependent PF and time independent PD health state utility values in MajesTEC-1	In the absence of PomDex utility data for patients with TCE RRMM, in the base case analysis, HSUVs for PomDex are informed by the accepted values used for PomDex in TA510[38]/TA783[8]. This scenario analysis explores an alternative source of utility data for PomDex, in line with those used for teclistamab given these are based on TCE RRMM patients. As there are no data to suggest that utilities vary over time for patients treated with PomDex, the HSUV for PF was modelled to be time-independent (see Section B.3.4.5)

7b: Health state utility values	PomDex and teclistamab HSUVs are informed by the time-independent PF and PD health state utility value in MajesTEC-1	This scenario analysis explores an alternative source of utility data for PomDex, aligned to those used for teclistamab in the base case analysis, including the use of time-dependent PFS utility values from MajesTEC-1. As detailed in Section B.3.4.5, given that the variations in utility over-time observed in the MajesTEC-1 trial are likely to be associated with the observed deepening of responses over time (see Section B.2.6.1) and only a very small proportion of patients receiving PomDex are likely to achieve CR, a similar deepening of responses and subsequent improvement in HRQoL over time on PomDex is unlikely. As such, the consideration of time-dependent utilities for the PFS health state for PomDex is considered highly conservative.
8a: Teclistamab subsequent treatments	Teclistamab Subsequent Treatment Distribution: Informed by the HDI study	In the base case, the costs of subsequent treatment are informed by the subsequent treatments in MajesTEC-1, adjusted for subsequent treatments which do not represent routine UK clinical practice (Section B.3.5.4). In this scenario analysis, the use of the subsequent treatments in the UK RW TCE cohort study are used to inform the costs of subsequent treatment following teclistamab.
8b: Teclistamab subsequent treatments	Proportion of patients receiving subsequent treatment after teclistamab is based on MajesTEC-1 (70.0%)	In the base case, the proportion of patients receiving subsequent treatment after teclistamab is based on Djebbari et al. (2020)[153], in line with previous precedent for NICE appraisals in RRMM. In this scenario analysis, the proportion of patients receiving subsequent treatment is assumed to be 70%, based on the MajesTEC-1 trial.
9: PomDex subsequent treatments	Subsequent treatment duration for PomDex is assumed to be half of that for teclistamab	In the base case, it is assumed that the duration of subsequent treatment following either teclistamab or PomDex is 4 months, based on Yong et al. (2016). This scenario explores the impact of assuming a shorter duration of subsequent treatment for PomDex, with the expectation that patients are less fit and have fewer subsequent treatment options available following PomDex, compared to

		teclistamab (where patients are able to receive PomDex as a subsequent treatment option).
10a	No Ig included in model	In the base case, Ig usage was aligned with that observed in the MajesTEC-1 trial. However, owing to feedback received during the draft scope consultation for this appraisal of ongoing national shortages of Ig,[199] this scenario explores the impact on the base case results when Ig is not utilised.
10b	Ig usage in MajesTEC-1 restricted to align with UK policy laid out by the NHS clinical commissioning group (patients with hypogammaglobulinemia and IgG < 4g/L, recurrent/severe bacterial infection and vaccine challenge)	This scenario explores the impact of aligning Ig usage with that anticipated in UK clinical practice (i.e., in line with the eligibility criteria outlined by the NHS Clinical Commissioning Group [patients with hypogammaglobulinemia and IgG < 400 mg/dL, recurrent/severe bacterial infections and vaccine challenge]).[186] While the IgG levels in the trial could not be matched exactly to the guidelines and evidence of vaccine rechallenge difficult to document given how the data was collected, the scenario remains more encompassing than current UK clinical practice and is thus more conservative.
11a	An illustrative tender price for tocilizumab is included	A tender price for tocilizumab has recently been agreed for use within the NHS (commencing March 2024).[200] While this tender price is confidential, this scenario applies a 80% discount to the cost of tocilizumab to explore the potential impact of this illustrative tender price.
11b	An illustrative tender price for tocilizumab is included	A tender price for tocilizumab has recently been agreed for use within the NHS.[200] While this tender price is confidential, this additional scenario applies a 90% discount to the cost of tocilizumab to explore the potential impact of this illustrative tender price.
12	Dose switching of all patients remaining on Q1W dosing after Year 1 on teclistamab to Q2W	In the base case analysis, a dose switching curve was used to estimate the proportion of patients switching to Q2W dosing over time. The remaining patients were assumed to remain on the weekly dosing regimen. This scenario assumes all

		patients remaining on treatment with teclistamab after one year switch to the Q2W dosing, in order to more accurately reflect patient and clinician preference for Q2W dosing. Full details of the rationale behind this scenario analysis are provided in Section B.3.3.5
13	Drug wastage for teclistamab is assumed to be 25%	In the base case, it is assumed that vial sharing is prevalent but 15% of each vial of teclistamab would be wasted, in line with the NICE appraisal for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies (ID2701).[22] Once reconstituted, the shelf life of teclistamab (20 hours) is longer than the shelf-life of belantamab mafodotin (4 hours), so assuming 15% wastage is reasonable.[184] Nevertheless, to explore the impact of this assumption, this scenario assumed that 25% of each vial of teclistamab would be wasted.

Abbreviations: AE: adverse events; ASCT: allogenic stem cell transplant; ATE: average treatment effect; ATT: average treatment effect for the treated; HSUV: health state utility values; INHB: incremental net health benefit; INV: investigator assessed; IVig: intravenous immunoglobulin; ICR: independent review committee; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; SC: subcutaneous; TA: technology appraisal; TTD: time to treatment discontinuation.

Table 82: Scenario analysis results for teclistamab versus PomDex (probabilistic; TEC PAS price, 1.2x severity modifier applied)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
1a	Teclistamab PFS: Informed by INV-assessed PFS	[redacted]	[redacted]	[redacted]	[redacted]	-£1,515	0.01	0.06
1b	Teclistamab PFS: Informed by IRC PFS	[redacted]	[redacted]	[redacted]	[redacted]	-£367	0.01	0.02
2a	Teclistamab PFS Adjustment: Adjusted to match the upper limit of the clinical expert estimates of survival (8% at 10 years, 2% at 15 years)	[redacted]	[redacted]	[redacted]	[redacted]	-£82	0.04	0.04
2b	Teclistamab PFS Attenuation: Adjusted to match the lower limit of the clinical expert estimates of survival (2% at 10 years, 0% at 15 years)	[redacted]	[redacted]	[redacted]	[redacted]	-£65	-0.05	-0.05
3	PomDex PFS: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£664	0.00	-0.02
4a	Teclistamab OS attenuation: adjusted to match	[redacted]	[redacted]	[redacted]	[redacted]	£336	0.20	0.19

	the upper limit of the clinical expert estimates of survival (15% at 10 years, 5% at 15 years)							
4b	Teclistamab OS Attenuation: Adjusted to match the lower limit of the clinical expert estimates of survival (5% at 10 years, 1% at 15 years)	[redacted]	[redacted]	[redacted]	[redacted]	-£382	-0.22	-0.21
5	PomDex OS Extrapolation: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£223	0.07	0.06
6	Teclistamab TTD: Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£2,291	0.00	-0.08
7a	PomDex and teclistamab HSUVs are informed by the time dependent PFS and PD health state utility values in MajesTEC-1	[redacted]	[redacted]	[redacted]	[redacted]	£0	-0.17	-0.17
7b	PomDex and teclistamab HSUVs are informed by the time independent PFS and PD health state utility value in MajesTEC-1	[redacted]	[redacted]	[redacted]	[redacted]	£0	-0.22	-0.22
8a	Teclistamab Subsequent	[redacted]	[redacted]	[redacted]	[redacted]	£360	0.00	-0.01

	Treatment Distribution: Informed by the UK RW TCE cohort study							
8b	Proportion of patients receiving subsequent treatment after teclistamab is based on MajesTEC-1 (70.0%)	[redacted]	[redacted]	[redacted]	[redacted]	£444	0.00	-0.01
9	Subsequent treatment duration for PomDex is assumed to be half the subsequent treatment duration for teclistamab (4 vs 2 months)	[redacted]	[redacted]	[redacted]	[redacted]	£956	0.00	-0.03
10a	No Ig included in model	[redacted]	[redacted]	[redacted]	[redacted]	-£4,254	0.00	0.14
10b	Ig use in line with UK clinical practice	[redacted]	[redacted]	[redacted]	[redacted]	-£2,086	0.00	0.07
11a	An illustrative tender price of 80% for tocilizumab is included	[redacted]	[redacted]	[redacted]	[redacted]	-£895	0.00	0.03
11b	An illustrative tender price of 90% for tocilizumab is included	[redacted]	[redacted]	[redacted]	[redacted]	-£1,006	0.00	0.03
12	Dose switching of 100% patients	[redacted]	[redacted]	[redacted]	[redacted]	-£3,345	0.00	0.11

	receiving teclistamab at year 1 remaining on Q1W dosing to Q2W							
13	Drug wastage for teclistamab is assumed to be 25%	[redacted]	[redacted]	[redacted]	[redacted]	£1,954	0.00	-0.07

Abbreviations: HDI: health data insight; HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; Ig: immunoglobulin; INHB: incremental net health benefit; INV: investigator assessed; IVig: intravenous immunoglobulin; IRC: independent review committee; OS: overall survival; PFS: progression-free survival; PD: progressed disease; QALY: quality-adjusted life year; TTD: time to treatment discontinuation; UK: United Kingdom.

B.3.12 *Subgroup analysis*

As noted in Section B.1.1, no subgroups were considered relevant to this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

B.3.13 *Benefits not captured in the QALY calculation*

Introduction of a novel class of MM treatment

The UK MM treatment pathway currently consists of three main classes of treatment (PI, IMiD, anti CD38 mAb). Triple-class-exposed RRMM emerges after all effective therapies have failed; therefore, patients have an acute and very high unmet medical need for a new class of medicines to control their illness and extent their life expectancy.

The reimbursement of teclistamab, a first-in-class T-cell engaging bispecific antibody technology, would introduce a novel class of MM treatments in the UK – the first new class of treatment since the introduction of anti-CD38 mAbs over 5 years ago.[38] The innovative mechanism of action demonstrated by teclistamab monotherapy would represent a significant step-change in managing relapsed/refractory multiple myeloma patients.

Value of hope associated with new treatment achieving deep and durable responses

In the MajesTEC-1 trial, teclistamab, an off-the-shelf immunotherapy treatment, achieved impressive overall response rate (ORR) of 63.0%, which is only surpassed by those observed with talquetamab and CAR-T cell therapies in this setting (Section B.2.6.1), both of which are not yet available in the UK pathway. Responses to teclistamab are deep and durable, with 46.1% of patients experiencing a ≥CR in MajesTEC-1. Among patients achieving ≥CR, the median DOR, PFS and OS were all NE at the latest DCO, with a 24-month OS rate of 82.8% (95% CI: [redacted], [redacted]%) for patients in CR or better – highlighting the potential for long-term survival with teclistamab.

As such, teclistamab offers patients a treatment option with deep and durable responses and long-term survival, in a patient population who would otherwise near the end of their terminal illness and face the prospect of receiving salvage therapy with previously trialled regimens. The value of hope for effective therapy, offering prolonged remission at a good quality of life associated with teclistamab cannot be fully captured in the economic model.

The acknowledgement of the significant unmet need in this patient population approaching the end of life, with a disease that has become resistant to conventional therapies, and the recognition of the value that a novel treatment option like teclistamab can provide is in the comments received during the consultation of the teclistamab draft scope. As acknowledged by Myeloma UK:

"*Despite approvals for treating myeloma in recent years, given the heterogeneity of the disease an unmet need remains*" (p6, Consultation Comments).

(…) "*as a B cell maturation antigen (BCMA) targeted T-cell engager, [teclistamab] would introduce a novel treatment approach into the pathway. As well as giving refractory patients hope, it also gives patients who may have never experienced complete response or lengthy remissions an opportunity to do so. The response rates for teclistamab are relatively high compared to other treatments for multiply relapsed myeloma patients. Responding well to a treatment has a huge psychological impact on patients and their families. [Further], this is a dexamethasone free treatment. Dexamethasone has a significant impact on the daily lives of patients. It causes mood swings, aggression, mania, insomnia and fatigue. This is difficult for patients and their families to live with."* (p21, Consultation Comments).

The importance of hope and the desirability of treatment choice for these patients was highlighted by a Myeloma UK study, where patients noted that running out of treatment options is a serious concern and highlighted the importance of offering more treatment choices at fourth line and beyond.[37] This would also help to resolve the current inequality in access to novel treatments throughout the MM pathway in the UK; as numerous novel treatments have been recommended in earlier lines of MM in recent years, yet there remains a dearth of innovation in the TCE RRMM setting.

Underestimated survival benefits in post-COVID-19 pandemic

The impact of COVID-19 excess mortality on the MajesTEC-1 trial is a significant consideration that cannot be fully captured in the QALY framework. The trial took place during the height of the COVID-19 pandemic, and 18 out of 94 deaths (10.9%) during the trial were attributed to COVID-19. In current clinical practice, with the widespread availability of vaccinations, these deaths would likely be preventable. While it is challenging to quantify the precise impact of this on teclistamab OS, it highlights an important benefit that cannot be captured adequately in the QALY measurement.

Opportunity to continue derive benefits from future innovations

Patients also face uncertainty about when and how future advances in medicine will occur, making life extension a valuable option that allows patients to potentially benefit from these unpredictable future advancements. This concept of a "real option value" arises when a life-extending health technology creates opportunities for patients to reap benefits from future medical progress.[201] This notion is particularly relevant in the case of teclistamab, considering the rapidly evolving treatment landscape in RRMM, where several ongoing clinical trials have showcased the potential of novel therapeutic agents like CAR-T cell therapies, bispecific antibodies and antibody-drug conjugates for heavily pre-treated patients.[104] The introduction of teclistamab could mean that patients who respond to treatment might live long enough to derive further benefits from subsequent innovative treatment options as they become available in the UK. However, these additional QALYs stemming from potential future benefits are currently excluded from the analysis.

Reimbursement of teclistamab in the UK for triple-class exposed RRMM population would optimise the future treatment pathway by facilitating the introduction of other (recently) approved novel treatments, such as talquetamab, into a similar positioning within the pathway. Conversely, the absence of a reimbursement for teclistamab, combined with the generic availability of pomalidomide later in 2024, would substantially limit the ability of non-generic medicines to demonstrate cost-effectiveness in this setting. This would increase the disparity between the UK and other European markets where novel treatments are routinely reimbursed and becoming the standard of care for TCE RRMM patients.

In summary, the value of hope, the true survival benefit with teclistamab in a post COVID-19 world and the priming of the treatment landscape for future innovations are all critical benefits of teclistamab that cannot be fully captured in the economic analysis.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Face validity

Model validations were performed in alignment with best practices.[202] The model structure, source data and statistical analysis design were reviewed by external experts, including health economic and UK clinical experts in MM.[203] Of note, and as discussed in Section B.3.3, a thorough validation process was conducted in order to inform the derivation and selection of base case extrapolations used in the economic analysis.

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,[204] 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.

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

The MajesTEC-1 trial demonstrated the efficacy of teclistamab in a challenging, heavily pre-treated, and high-risk triple-class exposed RRMM population. With an impressive ORR of 63.0%, teclistamab resulted in approximately double the number of patients achieving a response compared to PomDex. However, focusing solely on ORR understates the true benefits of teclistamab, as it induces substantially deeper responses in patients compared to PomDex. In MajesTEC-1, 59.4% of patients receiving teclistamab achieved a VGPR or better, including 46.1% who achieve a CR or better. This is a greater than 7-fold increase in the VGPR rate for teclistamab versus PomDex, as detailed in Section B.2.12.

These deep and durable responses observed with teclistamab resulted in substantial improvements in PFS and OS that were both statistically significant and clinically meaningful. The indirect treatment comparison revealed that teclistamab was associated with a hazard ratio of 0.52 for OS and an HR of 0.56 for PFS. These findings translate to a remarkable 48% reduction in risk of death and a 44% reduction in the risk of progression.

These compelling efficacy results were reflected in the base case economic analysis, where teclistamab was associated with a substantial increased [redacted] LYG and [redacted] QALYs versus PomDex. The QALY shortfall analysis revealed that patients with TCE RRMM are facing a severe unmet need under the standard of care within the NHS as evidenced by a substantial QALY shortfall of [redacted] representing the proportion of future health that patients with TCE RRMM lose over their remaining lifetime. Taking into account the 1.2x severity modifier, teclistamab was

associated with [redacted] incremental QALYs versus PomDex. This result underscores the potential for teclistamab to improve both the quality and duration of life for TCE RRMM patients who have exhausted all main treatment options and near the end of their terminal illness.

These economic results omit important benefits that cannot be captured in the QALY, including the value of hope and real option value, as well as the impact of COVID-19 excess mortality on the MajesTEC-1 trial, which all mean that the base case results are likely to represent a conservative estimate of the true cost-effectiveness of teclistamab in UK clinical practice (see Section B.3.13).

The economic evaluation used the best available clinical evidence for teclistamab. In the base case probabilistic and deterministic analyses, these clinical results translated to teclistamab representing a cost-effective treatment option compared to PomDex; at PAS price, teclistamab was found to be [redacted] versus PomDex in both the deterministic and probabilistic analyses, regardless of whether a severity modifier was applied. Thus, teclistamab can be considered a cost-effective use of NHS resources in RRMM patients after at least three prior therapies. Additionally, the positive INHB indicates that teclistamab not only provides additional clinically meaningful health benefits to TCE RRMM patients but does so in a cost-effective manner over existing standard of care with PomDex. The substantial value of INHB supports the case for adopting teclistamab over PomDex.

The PSA found the probability of teclistamab being cost-effective to be [redacted] and [redacted] at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The DSA results identified a small number of key influential parameters including, the mean body weight of patients, the final time-dependent utility value for the PF state and the PD HSUV. However, overall, the base case results were found to be robust to uncertainty across all model parameters. Scenario analyses conducted to address sources of uncertainty in the model demonstrated that variations in the INHB were minimal. Importantly, none of the scenario analyses resulted in changes to the cost-effectiveness conclusions of the base case analysis; teclistamab remained [redacted] versus PomDex across all scenarios.

Strengths

A robust clinical validation exercise was conducted by Janssen with four clinical experts and three health economic experts in the UK in order to validate key inputs and assumptions, including monitoring frequencies, utility inputs, subsequent treatment options as well as elicit plausible long-term survival estimates.[203] Furthermore, as outlined in Section B.3.3.2, none of the survival estimates generated by the standard parametric functions were able to simultaneously fit closely to the observed OS and PFS data from MajesTEC-1, while also provide plausible long-term estimates of survival that were aligned with predictions provided by UK clinical experts. As such, the economic model adopts a bespoke approach, whereby the statistically best fitting PFS and OS curves for teclistamab are subsequently attenuated over time to directly align with long-term estimates of survival provided by UK clinical experts. This novel approach ensured that survival estimates for teclistamab included in the model were associated with both high internal and external validity, which would otherwise not have been possible. Additionally, the clinical experts reviewed the baseline characteristics of patients enrolled in MajesTEC-1 and the UK RW TCE cohort study, both of which were deemed representative of UK clinical practice. The results

of the economic analysis are therefore considered highly relevant to decision-making on the introduction of teclistamab into NHS clinical practice.

The cost-effectiveness analysis is associated with several strengths, the first being that many therapies for RRMM have been appraised by NICE.[4, 38, 163] A review of relevant NICE evaluations was conducted during model design and development, and thus it was 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), such as cost and resource use and the selection of HSUVs.

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.[205]

Limitations

A key limitation of the evidence base was the lack of direct data comparing teclistamab to the relevant comparator in UK clinical practice (PomDex). To address this limitation, Janssen commissioned a UK RW TCE cohort study to obtain IPD for PomDex and an ITC was conducted in order to obtain relative efficacy estimate of teclistamab versus PomDex (see Section B.2.9). The ITC was conducted in line with the best practices outlined in NICE TSD 17 when IPD are available for all treatments included in the ITC.[156] Furthermore, as in the base case analysis IPD from the MajesTEC-1 trial was adjusted to align with the PomDex cohort from the NCRAS database (which contains national real-world data on patients who would use teclistamab in UK clinical practice), the results of the ITC are considered as highly relevant to decision-making. Uncertainty surrounding the 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 (B.3.11).

Due to the median follow-up of MajesTEC-1 being shorter than the total time horizon, long-term extrapolation of the PFS and OS data from the MajesTEC-1 trial were required, which is inevitably associated with uncertainty. However, this uncertainty was mitigated by the fact that survival data obtained from the latest DCO of MajesTEC-1 were relatively [redacted], with median OS reached. To address this limitation, as noted in Section B.3.3.2, selection of the most appropriate parametric survival functions followed the recommendations outlined by the NICE DSU TSD 14.[206] Specifically, selection was informed by a combination of goodness-of-fit statistics, inspection of visual fit (internal validity) as well as feedback received from clinical experts on the relative clinical plausibility of each curve (external validity). Furthermore, uncertainty surrounding the long-term survival estimates of teclistamab were explored in several scenario analyses which demonstrated the base case results to be robust to variations in these estimates (Section B.3.11.3).

Conclusion

A critical unmet need exists for novel and effective therapies to be made available for triple-class exposed RRMM patients. These patients experience significant burden on their health-related quality of life and face an extremely poor prognosis, with a median OS as short as 9.78 months (95% CI: 8.64 to 10.82 months).[24] Modelling estimates suggest that teclistamab could increase LYG by [redacted] and QALY by [redacted] QALYs compared to PomDex. The latter could rise to [redacted] once the severity modifier is incorporated.

Recommending the use of teclistamab in this patient population would address the current unmet medical and patient need for an effective novel treatment option which can better control disease and provide deeper, more sustained responses, ultimately leading to improvements in patient HRQoL and prolonging survival.

Overall, considering the PAS price, the base case ICERs for all comparisons demonstrated teclistamab to be cost-effective at a WTP £30,000 per QALY, making teclistamab a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Addendum to Company submission

May 2024

File name	Version	Contains confidential information	Date
ID6333_Teclistamab_Addendum_V1.0 [CON].docx	1.0	Yes	21 May 2024

Introduction

Johnson & Johnson Innovative Medicine (previously Janssen) would like to thank NICE for accepting this short addendum to the Company submission. The purpose of this addendum is to provide additional scenarios around the use of therapeutic immunoglobulin in patients treated with teclistamab. This is to support Committee decision making by exploring the impact that variations in therapeutic immunoglobulin use may have on the incremental cost-effectiveness of teclistamab. These scenarios are presented in Section B1.

In addition, Johnson & Johnson Innovative Medicine have amended the company base case to further align with the EAG base case (see Section A) and presented additional evidence on the topic of drug wastage gathered from early use of teclistamab in the UK in the single patient request programme (see Section B2).

We hope that this addendum is useful to support a recommendation for teclistamab in the triple-class exposed, relapsed refractory multiple myeloma patient population addressing the critical unmet need for treatments that may prolong survival and improve quality of life.

Section A: Change(s) to the Company's base case

In addition to this addendum, Johnson & Johnson Innovative Medicine have submitted an updated confidential simple patient access scheme (PAS) of [redacted] for teclistamab. The impact of this updated PAS on the base case Company results is presented in Table 1 below. This leads to a change in the Company base case INHB of [redacted]. All subsequent results presented in this addendum take into consideration this updated PAS.

Table 1. Impact of updated PAS on Company base case results (deterministic, TEC PAS price, 1.2x severity modifier applied)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Company clarification base case with updated PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue 7: Application of a one-off utility decrement for patients who experience TEAEs represents double counting

The Company base case included adverse event disutilities. Utility decrements due to AEs were sourced from publications and previous HTA submissions (see Company submission (CS) Table 51). The duration of utility decrements was based on MajesTEC-1. Utility decrements were applied as one-time decrements in baseline utility value at the start of the partitioned survival model. The EAG base case excluded this adjustment based on the MajesTEC-1 trial HRQoL dataset already including data from patients who experienced AEs.

In response to the EAG report, Janssen has revised the company economic model to remove the TEAE disutility values, and therefore the impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

Key issue 8: Proportion of patients treated with teclistamab who receive subsequent treatment

The Company base case assumed that 52.6% of patients go on to receive a subsequent treatment following disease progression on teclistamab or PomDex based on Djebbari et al. (2020), a real-world study of UK MM patients[1]. This approach is consistent with the Committee's preferred assumptions used in NICE TA889 (cilta-cel appraisal) and NICE TA658 (IsaPomDex appraisal). A scenario was included in the company submission to explore the impact of using MajesTEC-1 trial data to inform the proportion of subsequent treatments in the teclistamab arm, i.e. ([redacted] %)[2] (see CS scenario 8b).

The EAG report considered that the proportion should reflect the experience of the MajesTEC-1 trial teclistamab population rather than on real world study data (i.e., the aforementioned scenario analysis).

While either approach is plausible and may have been accepted in previous appraisals, Janssen has revised the company economic model to update the model according to the EAG preference. The impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

Key issue 9: Subsequent treatments should reflect NHS practice

The Company submission presented all the reasonable adjustments that were taken to ensure that the subsequent treatments costed in the economic model were reflective of NHS practice (see CS, Section B.3.3.2 and Section B.3.5.4).

In both MajesTEC-1 and the UK RW TCE cohorts [2,3], there were instances of patients receiving subsequent regimens which are not routinely available in UK clinical practice (see Table 67 in CS). In order to ensure subsequent treatment costs were reflective of the UK treatment pathway, the subsequent treatment distributions in both studies were re-weighted to remove subsequent treatments not routinely available in the UK and/or after 3 prior therapies e.g. talquetamab, cilta-cel, carfilzomib, belantamab (see Table 68 in CS). Additionally, overall survival in the teclistamab arm was further adjusted using the advanced "two-stage" method described in NICE TSD 16 [4] for the possible effects of subsequent treatments in the MajesTEC-1 trial not currently routinely available in UK clinical practice, which might have the potential to increase the predicted long-term estimates of survival. No OS adjustment was undertaken in the PomDex arm as a conservative approach.

Based on clinical advice that choice of subsequent treatment is unlikely to affect clinical outcomes, the EAG report discarded the empirical MajesTEC-1 trial data and instead equalised the distribution of subsequent treatments received by triple-class exposed relapsed/refractory multiple myeloma (RRMM) patients across both teclistamab or PomDex arms, with the exception that some patients initially treated with teclistamab receive a proportion of PomDex as a subsequent treatment as observed in the MajesTEC-1 trial ([redacted] %).

While either approach is plausible, and may have been accepted in previous appraisals (e.g. TA889, TA658), Janssen has revised the company economic model to update the distribution of subsequent treatments received by MajesTEC-1 trial patients and PomDex patients in line with the EAG approach. The impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

A summary of the changes to the Company's base case can be found below in Table 2. Combined, key issues 7, 8 and 9 lead to an updated INHB of [redacted] compared to the Company base case INHB of [redacted] .

Table 2. Summary of change(s) to the Company's clarification base case in response to the EAR (deterministic, updated TEC PAS price, 1.2x severity modifier applied)

Key issue(s) in the EAR that the change relates to	Company's clarification base case before EAR	Change(s) made in response to EAR	Impact on the Company's base-case
Key Issue 7: Application of a one-off utility decrement for patients who experience TEAEs represents double counting	In the original CS, a one-off TEAE disutility was applied in line with literature and previous appraisals (e.g. TA171, TA573, TA559, TA510).	Janssen has updated the economic model to remove TEAE disutility.	Base case INHB (Mar 2024): [redacted] Impact of removing TEAE disutility (May 2024): [redacted]
Key Issue 8: Proportion of patients treated with teclistamab who receive subsequent treatment	In the original CS, the proportion of patients receiving subsequent therapies was assumed to be 52.6% in both teclistamab and PomDex arms, based on a UK RWE report by Djebarri et al (2020) and previous appraisals (TA889, TA658).	Janssen has updated the proportion of subsequent treatments for patients treated with teclistamab ([redacted] %).	Base case INHB (Mar 2024): [redacted] Impact of updating the proportion of subsequent treatments (May 2024): [redacted]
Key Issue 9: Subsequent treatments should reflect NHS practice	In the original CS, the distribution of subsequent treatments was informed by both MajesTEC-1 trial and the UK RW TCE cohort study.	Janssen has updated the distribution (and frequencies) of subsequent treatments so that these are the same for patients treated with teclistamab and PomDex, with further adjustment to the proportion of PomDex as a subsequent treatment for patients treated with teclistamab.	Base case INHB (Mar 2024): [redacted] Impact of adjusting the distribution of subsequent treatments (May 2024): [redacted]
Key issues 7, 8 and 9 combined	-	-	Base case INHB (Mar 2024): [redacted] Updated INHB (May 2024): [redacted]

CS: Company submission; **TA**: Technology appraisal; **TEAE**: treatment-emergent adverse event; **INHB**: incremental net health benefit; **RW/RWE**: real-world evidence; **TCE**: triple-class exposed

Section B: Additional scenarios

B1. Immunoglobulin use

Context

Use of therapeutic immunoglobin, a feature of the teclistamab cost-effectiveness model, has been a topic of discussion in several NICE appraisal committee meetings, including appraisals focused on RRMM treatments. In light of these discussions, and recognising the urgent clinical unmet of the TCE RRMM patients alongside our common objective of obtaining positive access for teclistamab as early as possible, we seek to further support the Committee's decision-making by offering supplementary analyses.

In our original submission and in response to clarification questions, we provided cost-effectiveness model results for scenarios involving lower IVIG use than in the base case. However, we have considered additional scenarios presented below in this addendum to provide further insights into the potential impact on the INHB (through varying costs) when increased IVIG use is considered, to a reasonable upper limit.

Our position is that the use of IVIG as per the base case, which is based on the MajesTEC-1 trial provides the most robust, data-driven evidence for decision making. This is because the efficacy and safety of teclistamab in the economic model are also derived from MajesTEC-1. Thereby, using MajesTEC-1 to inform efficacy, safety and IVIG use ensures internal consistency of the model results. There is a growing body of evidence that usage of IVIG reduces infection with BCMA-targeting bispecifics [5-7]. As correctly noted by the EAG during the clarification stage, it is not reasonable to simply adjust costs or outcomes without adjusting both appropriately; this results in overly optimistic or pessimistic scenarios depending on the direction of adjustment. Thus, we consider the scenarios presented in this addendum a highly conservative approach, given that only costs of additional IVIG use have been modelled without any adjustments to clinical outcomes.

Finaly, we note the scope of this appraisal defines teclistamab as the intervention under question (not teclistamab in combination with IVIG). The evidence provided in the submission and included in the economic model relates to teclistamab as it was studied in MajesTEC-1. Whilst we acknowledge that there is uncertainty regarding the use of IVIG alongside bispecific antibodies, our position is that the clinical and cost-effectiveness of IVIG is a decision problem in its own right and outside the scope of this appraisal. The evidence we have provided is sufficient to demonstrate that teclistamab used as per trial is clinically and cost-effective compared to PomDex. We are keen to avoid scope creep precluding patient access to teclistamab owing to uncertainty regarding use of IVIG, and indeed the cost-effectiveness of IVIG.

Additional Analyses

The SmPC for teclistamab [8] indicates that severe, life-threatening, or fatal infections have been reported in patients receiving teclistamab. Patients should be monitored for signs and symptoms of infection prior to and during treatment with teclistamab and treated appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines. In case of Grade 3 or greater infections, the SmPC recommends withholding subsequent maintenance doses of teclistamab until infection improves to Grade 2 or better. Immunoglobulin levels should be monitored during treatment with teclistamab and it is noted that immunoglobulin replacement therapy was administered in 39% of patients.

Therapeutic immunoglobulin is recommended to be available as a routinely commissioned treatment option in NHS England for secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment for 6 months and either proven specific antibody failure or serum level of IgG <4 g/L (excl. paraprotein) [9]. If approved by panel, the standard clinical practice is to dose at 0.4g/kg/month and, based on mean bodyweight of [redacted] kg in MajesTEC-1, a dose of 30g would be administered every 4 weeks. Six (6) monthly reviews (compared to baseline) are expected to be documented and an annual review is recommended to assess whether the patient still benefits from Ig treatment. For patients who are more susceptible to seasonal infections (like myeloma patients who are suffer most from respiratory infections), the policy considers appropriate to temporarily cease Ig therapy over the summer months.

In the NHS England budget impact analysis (BIA) submission for teclistamab (Jan 2024), it is acknowledged that the duration of treatment with immunoglobulin is variable and hard to predict. Based on clinical advice received from NHSE, nine (9) administrations were modelled in the BIA.

In line with the BIA, the Company presents additional scenarios varying the duration of IVIG use with teclistamab to explore impact of this uncertainty (i.e. 6, 9 and 10 doses) for 2 assumptions on the proportion of patients receiving IVIG, i.e. 39% as per the BIA/SmPC or [redacted] % as per the Company base case (based on MajesTEC-1).

A complete list of the scenarios explored and impact on both the Company base case and the EAG Base case INHB is provided in Table 3 below.

Table 3. Summary of scenario analyses on IVIG use with teclistamab (deterministic, updated TEC PAS price, 1.2x severity modifier applied)

	Description of the scenario	Company clarification base case INHB at £30,000 (including key issues 7, 8 and 9)	EAG base case INHB at £30,000
0	Base case INHB at £30,000	[redacted]	[redacted]
1a	39% patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
1b	39% patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
1c	39% patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]
2a	[redacted] % patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
2b	[redacted] % patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
2c	[redacted] % patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]

IVIG: intravenous immunoglobulin; **EAG**: External Assessment Group; **INHB**: incremental net health benefit

B2. Drug wastage

The company submission assumed that drug wastage will be limited in the delivery of teclistamab based on assumption that vial sharing is encouraged by NHS England (TA862, TA819, TA704) and previous appraisals in RRMM where drug wastage assumptions were accepted (TA658).

In the base case, it is considered that vial sharing occurs in NHS practice and therefore, 15% drug wastage for teclistamab is assumed, in line with the NICE appraisal for belantamab mafodotin for treating RRMM after 4 or more therapies (ID2701). Once reconstituted, the shelf life of teclistamab (20 hours) is longer than the shelf-life of belantamab mafodotin (4 hours), so assuming 15% wastage is conservative. The company submission included a scenario exploring the impact of 25% drug wastage for teclistamab.

Since the submission, Janssen has gathered information from the early use of teclistamab in the UK. In the UK single patient request programme (UK SPR), [redacted] TCE RRMM patients received teclistamab in this early access programme between March 2022 and February 2023 [10]. Vial sharing was not permitted, implying that drug wastage in the UK SPR would be higher than it would be in standard UK clinical practice, where vial sharing would be encouraged. Using patient-level data, the volume of drug wastage was estimated to be [redacted] % on maintenance doses ([redacted]% including step-up doses).

This new evidence supports a low drug wastage assumption with teclistamab, even in the conservative scenario where no vial sharing occurs, hence further supporting the base case assumption of drug wastage, and placing a plausible upper bound of ~25%.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

[ID6333]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6333_Teclistamab_NICE_SIP_noCON_5Feb2024	N/A	No	5th February 2024

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: Teclistamab

Brand name: TECVAYLI®

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 and refractory multiple myeloma (RRMM**; defined in **Section 2a**) The condition – clinical presentation and impact) 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.

When a patient has received all three of these **drug classes** of **multiple myeloma (MM)** therapies, they would be considered to be **triple-class exposed (TCE)**. 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. 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**) The condition – clinical presentation and impact.

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 November 2022, the **Medicines and Healthcare products Regulatory Agency** (**MHRA**) granted **marketing authorisation** for teclistamab administered **subcutaneously** (injected into the tissue between the skin and muscle), as a monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma after at least three prior anticancer 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 teclistamab in the same indication was granted by the **European Medicines Agency (EMA)** on 23rd August 2022 (2).

Further licensing information for teclistamab can be found on the respective websites:

- MHRA: https://products.mhra.gov.uk/search/?search=teclistmab&page=1
- EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/tecvayli

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:

Janssen has provided the following support to relevant patient groups in the United Kingdom (UK), as presented below in **Table 1**.

Table 1: Summary of support provided by Janssen to relevant patient groups

Patient group	Engagement/activity	Reason for engagement/activity	Financial support provided
Anthony Nolan	Janssen supported a CAR-T Patient Experience Survey Project commissioned by Anthony Nolan	Grant requested by patient organisation	£18,200.00
Anthony Nolan	Janssen supported Anthony Nolan with a grant of £29,245 to support the implementation of a Cell Therapies Nurse Specialist	Grant requested by patient organisation	£29,245.00

Blood Cancer UK	Janssen provided BCUK with a grant of £37,000 to support their work to address the issue of delayed diagnosis of blood cancer	Grant requested by patient organisation	£37,000.00
Blood Cancer UK	Janssen covered travel costs of £371.50 for Blood Cancer UK's involvement in a Janssen Haematology study day	Patient organisation attending Janssen event to demonstrate resources available to HCP's and their patients	£371.50
Blood Cancer UK	In 2022 Janssen supported BCUK with a financial grant of £25,000 towards their project reduce delayed diagnosis for Blood Cancer patients	Grant requested by patient organisation	£25,000.00
Blood Cancer UK	Janssen provided Blood Cancer UK with a grant of £45,380 towards the cost of delivering their National Blood Cancer Action Plan	Grant requested by patient organisation	£45,380.00
Cancer 52	In 2022 Janssen gave Cancer 52 £10,000 to support delivery of their core activities in 2022	Grant requested by patient organisation	£10,000.00
Cancer 52	In 2023 Janssen provided sponsorship of £10,000 to Cancer 52's Corporate Supporter Programme	Sponsorship requested by patient group	£10,000.00

Leukaemia Care	Janssen provided Leukaemia Care with a fee of £180 for participation in a Janssen Oncology Advisory Board	Patient organisation attending a Janssen advisory board to share expertise	£180.00
Leukaemia Care	Janssen covered travel costs of £53.30 for Leukaemia Care's involvement in a Janssen Haematology study day	Patient organisation attending Janssen event to demonstrate resources available to HCP's and their patients	£53.30
Leukaemia Care	Janssen gave Leukaemia Care £5,000 in support of their core activities for 2022	Grant requested by patient organisation	£5,000.00
Leukaemia Care	Janssen provided Leukaemia Care with a grant of £7,500 towards their Emotional Support Project in 2022	Grant requested by patient organisation	£7,500.00
Myeloma UK	Janssen gave Myeloma UK a grant of £25,000 towards their 'Supporting Patient Voices' project	Grant requested by patient organisation	£25,000.00
Myeloma UK	Janssen covered travel costs of £341.80 for Myeloma UK's involvement in a Janssen Haematology study day	Patient organisation attending Janssen event to demonstrate resources available to HCP's and their patients	£341.80

Myeloma UK	Janssen covered travel costs of £294.73 for Myeloma UK to attend a HTA Advisory Board.	Patient organisation attending a Janssen advisory board to share expertise	£294.73
Myeloma UK	Janssen gave Myeloma UK a grant of £25,000 to support the delivery of Patient Support Services	Grant requested by patient organisation	£25,000.00
Myeloma UK	Janssen paid a representative of Myeloma UK a fee of £180 to speak at a Janssen organised Medical Education Event for nurses.	Speaker fees for Myeloma expert speaker at a Janssen Event	£180.00
Myeloma UK	Janssen gave Myeloma UK a grant of £15,907 to support the delivery of Patient Support Services	Grant requested by patient organisation	£15,907.00
Myeloma UK	Janssen provided sponsorship of £9,093 to Myeloma UK by paying the entry fee for seven of its' employees to participate in the annual fundraising Ride Myeloma 2023 event	To allow Janssen employees to participate in a Myeloma UK organised charity bike ride	£9,093.00
Myeloma UK	Janssen provided Myeloma UK a fee of £660 for two representatives to attend a workshop looking at the Economic Burden of Multiple Myeloma.	For Myeloma UK representatives to contribute their expertise to a Janssen hosted policy workshop	£660.00

Specialised Health Care Alliance	Janssen 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	Sponsorship requested by patient group	£14,500.00

Abbreviations: CAR-T: chimeric antigen receptor-T cell; BCUK: Blood Cancer UK; HTA: health technology assessment; NHS: National Health Service; UK: United Kingdom.

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**. These plasma cells make **antibodies**, a type of **protein** that helps the **immune system** recognise and fight infections. 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 plasma cells in the bone marrow. Over time, this can lead to complications such as a weakened immune system, damage to the kidneys, bone disease and low levels of red blood cells (**anaemia**). This disease is referred to as MM as it affects a number of different areas of the body such as the spine, skull, pelvis and ribs (3).

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 2016 to 2018 in the UK (4). Owing to improvements in early detection and changes in risk factors, the number of people diagnosed with MM has increased by approximately 15% in the UK in the last 10 years (4). At any one time there are around 24,000 people living with MM in the UK (3).

MM more commonly occurs in people over the age of 60 years. It is also slightly more common in men (58%) than women (42%). Estimates in England also suggest that black people are twice as likely to get MM compared with white people (5, 6).

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 (7). 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 receive treatment from three different drug classes. These include:

- Immunomodulatory agents (IMiDs): these work by stimulating or suppressing the immune system to treat 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 allowing the immune system to target and kill the MM cells.

When a patient has received all three drug classes of standard MM therapies, they would be considered to be **triple-class exposed (TCE)**. For simplicity, this group of patients will be referred 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. Nevertheless, as new NHS treatment alternatives emerge in the early stages of the MM treatment pathway, it is expected that the proportion of patients with TCE RRMM will rise over time. Their MM is also likely to become refractory to current anticancer therapies, creating a significant need for a novel class of treatments capable of managing the rapidly evolving disease.

What is the impact of TCE RRMM?

Life expectancy

The impact of MM is different for each patient, depending on several factors. These include individual 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. On average, patients with MM are expected to live for six years following initial diagnosis (8). With each subsequent therapy that patients with MM do not respond to, they are estimated to live for a shorter period of time (8). There is a high unmet need for additional effective treatment options available in the UK for patients with TCE RRMM, with studies estimating that patients with TCE RRMM are only expected to live for an average of 7 to 10 months (9).

Symptoms of TCE RRMM and their physical impact

Patients with MM experience symptoms such as frequent and persistent infections, fatigue and bone pain, which often result in further complications that affect day-to-day activities (10). 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 (11). More than two thirds of all patients with MM also develop anaemia resulting in people feeling tired and weak, making it difficult to perform everyday tasks (12).

The progression of MM to RRMM intensifies the impact of the disease resulting in more severe and more numerous symptoms than those with newly diagnosed or stable MM (13). This is supported by the findings of a 2020 multi-centre 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 to treatment and exposure to multiple rounds of treatment. This is in line with the 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 experienced and felt more tired (14). These worsened symptoms experienced by patients with TCE RRMM have implications on their ability to perform day-to-day tasks. Examples of more frequently experienced symptoms include (13):

- Sore or dry mouth
- Diarrhoea
- Tingling in limbs
- Shortness of breath
- Difficulties remembering
- Bone pain
- Elevated calcium levels (hypercalcemia)
- Renal failure
- Low levels of red blood cells (anaemia)

Quality of life and psychological impact

In addition to the physical symptoms associated with the disease, MM also significantly impact patients' mental and emotional health. 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 quality of life in terms of physical and mental health, and vice versa.

A diagnosis of MM has substantial emotional distress on patients, 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 (15). Furthermore, uncertainty about the future causes persistent anxiety and often affects patients' relationships with family and friends who may act as informal caregivers (16, 17).

Additionally, an initial relapse in disease has been found to be associated with prolonged feelings of negative emotions such as hopelessness and resignation (16). With each subsequent relapse, patients feel more distressed and less hopeful as they may feel that available treatment options have been exhausted (16). Depression can also affect one in four patients with MM (18). As patients with RRMM experience a greater symptomatic

disease burden and are expected to live shorter than patients with MM, patients with RRMM experience worse HRQoL than patients with other cancer types (13, 19, 20).

As there is a lack of novel treatment options for TCE RRMM, patients with TCE RRMM experience more severe symptoms and physical impact, thereby resulting in particularly poor HRQoL. 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 (14).

Impact on families and carers

Caring for a person with MM is an all-encompassing role that requires dedicated time and that impacts 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 dressing or giving injections and help with other day-to-day activities (21). Carers may also accompany patients with MM to attend medical appointments which can also disrupt their employment, leading to missed work days increasing the financial impact felt by family members, who often act as informal carers (18).

Symptoms of anxiety (49%) and depression (14%) experienced by partners of patients with MM further impacts the emotional impact experienced by carers (18). 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 shorter life expectancy for patients with TCE RRMM, due to limited effective treatment options, leads to anxiety and emotional distress and places significant emotional burden on families and caregivers caring for patients with TCE RRMM (10).

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 MM 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. The three main types are as follows (22-24):

- Blood tests: as MM is typically characterised by the presence of abnormal M proteins, regular blood tests are performed to measure the levels of different cells and check for presence of these abnormal proteins in the blood.
- Imaging tests: as MM can lead to bone damage, imaging tests such as **X-rays**, **magnetic resonance imaging (MRI)**, **computerised tomography (CT)** scans, and **positron emission tomography (PET)** scans may also be used.

- **Bone marrow** samples: a small sample, known as a **biopsy**, of the bone marrow is taken, usually from the hip bone and examined under a microscope to identify whether abnormal proteins or cell counts are present.

2c) Current treatment options:

What are the current treatment options for TCE RRMM?

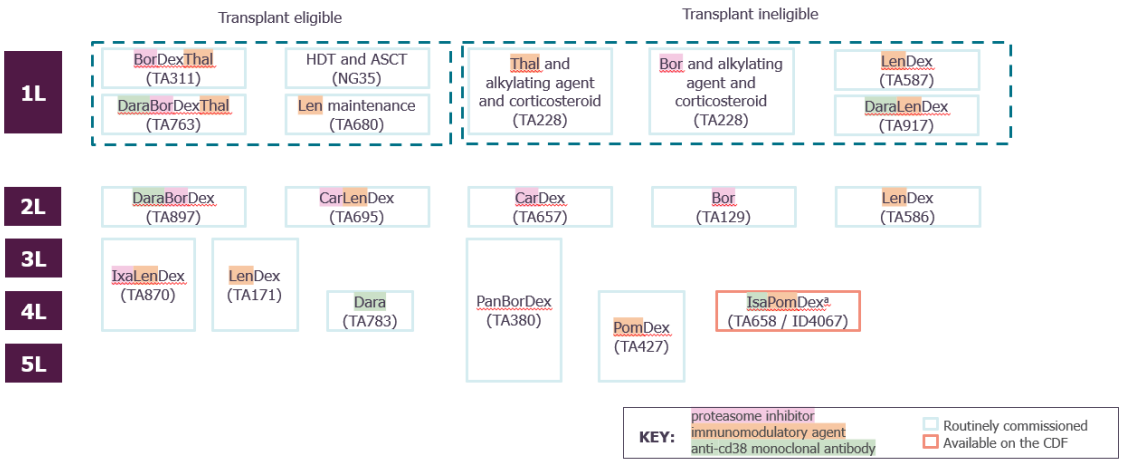
Treatment guidelines for the management of MM are available from the British Society of Haematology (BSH), European Haematology Association and European Society for Medical Oncology (EHA-ESMO), European Myeloma Network (EMN), National Comprehensive Cancer Network (NCCN) and the National Institute for Health and Care Excellence (NICE) (NG35) (25-28).

Whilst some of these guidelines provide recommendations specifically for patients with TCE RRMM, the majority of the recommended treatments are not accessible to patients with TCE RRMM in UK clinical practice. This is the result of treatments being withdrawn from/not approved for use during the UK drug approval process and/or treatments not being recommended by NICE. As such, the management of TCE RRMM in the UK is primarily informed by NICE guidelines for the treatment of RRMM [NG35] (29).

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 a SCT are typically treated with daratumumab (Darzalex®) in combination with bortezomib (Velcade®) and thalidomide (Thalomid®) (30). 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 (Revlimid®) and dexamethasone (31). The treatment options for MM are summarised and presented below in Figure 1.

Figure 1: The current NHS MM treatment pathway



[a] Patients eligible for IsaPomDex must have either not previously received treatment with an anti-CD38 mAb treatment, or not previously demonstrated disease progression while receiving an anti-CD38 mAb treatment. The full eligibility criteria for IsaPomDex through the CDF is available here: https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list--version-1.287.pdf. CDF refers to Cancer Drugs Fund which is a way of funding new cancer medicines in England before NICE considers approving these treatments for routine use in the NHS.
Abbreviations: 1/2/3/4L/5L: 1st/2nd/3rd/4th/5th line; ASCT: autologous stem cell transplantation; Bor: bortezomib; Car: carfilzomib; CDF: Cancer Drugs Fund; Dara: daratumumab; Dex: dexamethasone; HDT: high dose therapy; ID: identification number; Isa: isatuximab; Ixa: ixazomib; Len: lenalidomide; NICE: National Institute for Health and Care Excellence; Pan: panobinostat: Pom: pomalidomide; TA: technical appraisal; Thal: thalidomide.
Source: NICE Myeloma Diagnosis and Management (32).

Treatment of RRMM in the UK is highly individualised and dependent on a patient's eligibility and response to previous treatment, with patients receiving treatment with the following three drug classes in a varying order and in varying combinations: PI, IMiD, anti-CD38 mAb (33). Examples of treatments in these drug classes include, but are not limited to:

- PI: bortezomib (Velcade®) and carfilzomib (Kyprolis®) (34)
- IMiD: lenalidomide (Revlimid®), pomalidomide (Imnovid®) and thalidomide (Thalomid®) (35)
- Anti-CD38 mAb: daratumumab (Darzalex®) and isatuximab (Sarclisa®) (36)

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. This approach is taken because patients are unlikely to show a good clinical response to a drug from the same class that they have previously experienced disease relapse on.

As mentioned earlier, this NICE submission focuses on patients with MM who have been exposed to all three major drug classes of treatment and have shown disease progression on the last therapy received. Unfortunately, for this specific group of patients with TCE RRMM, there are no treatment options with novel modes of action in the UK. In practice, UK clinical experts indicated that patients with TCE RRMM predominantly receive pomalidomide in combination with low-dose dexamethasone, which represents re-

treatment with a next generation IMiD. Hope and treatment choice are very important to patients with MM and their families, and patients have expressed serious concerns about running out of effective therapies in the NHS.

The recommendation of teclistamab would therefore be transformative for the management of RRMM by introducing an effective treatment option with a novel mechanism of action for patients with otherwise limited effective treatment options.

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 quality of life. There have been a number of studies aiming to understand patient preferences for treatment whilst considering symptoms experienced and corresponding treatment benefits. However, as mentioned in **Section 2a**) The condition – clinical presentation and impact, given the population of patients with TCE RRMM is relatively small at the moment, there are few studies conducted specifically in this population which report on their symptoms and quality of life. 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 which affect their quality of life and ability to perform day-to-day tasks (14).

Studies reporting on HRQoL

A study in 445 French patients with symptomatic MM reported on their HRQoL scores assessed via the **European Organisation for Research and Treatment of Cancer Core Quality of Life (EORTC QLQ-30)** questionnaire (37). The results showed that the quality of life of patients with MM significantly decreased with each line of treatment failed (37). More heavily treated patients with MM such as patients with TCE RRMM would therefore, have worse HRQoL compared to patients who have received fewer lines of therapy (37).

A prospective international study in 248 patients with TCE RRMM assessed patient reported outcomes (14). This study also showed that as patients with MM progress through different treatment options their HRQoL, physical functioning, and symptoms of pain and fatigue worsen (14).

Studies reporting on treatment preference

A recent study of 300 patients with MM, including 98 patients with RRMM across France, Germany and the UK assessed their preference for 8 potential treatment benefits (38). A longer life expectancy and improvements in symptoms such as pain and tiredness were found to be the most valued benefits of a new treatment for patients with newly diagnosed MM (38).

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. Participants 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.(39) The value that patients with MM place on treatments that offer better control of the disease, longer life expectancy and improvements in symptoms would be even greater for patients with TCE RRMM who reach the end of the treatment pathway with a short life expectancy of 7 to 10 months and experience worsened symptoms as they receive more treatments (9). Teclistamab, a first in class immunotherapy, could provide patients dealing with TCE RRMM the hope of a extended life expectancy, addressing a substantial unmet need within this cohort of heavily pre-treated patients who face the dearth of effective and quality of life-preserving treatment alternatives towards the end of the MM pathway (40).

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.

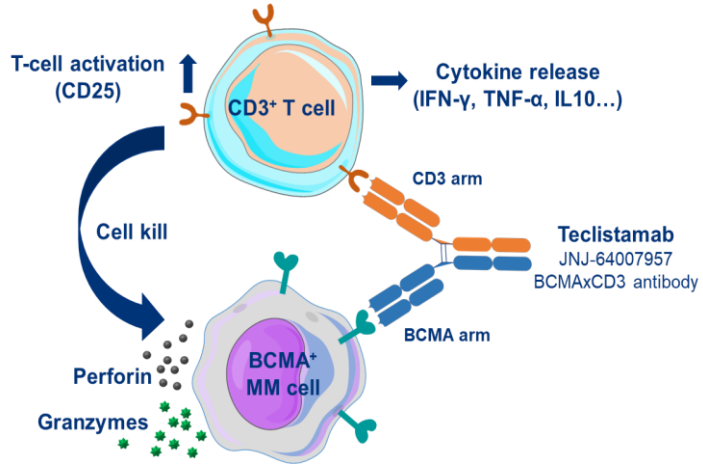
What is teclistamab and how does it work?

Teclistamab is a medicine that has been approved by the MHRA and is a type of **immunotherapy** which are therapies that help the immune system to recognise and kill cancer cells. Teclistamab is a **bispecific antibody** (a type of protein which has been designed to recognise and attach to specific targets in the body). It targets two different proteins, making it bispecific:

- **B cell maturation antigen (BCMA)**, which is found on multiple myeloma cancer cells
- **Cluster of differentiation 3 (CD3)**, which is found on specific cells in the body's immune system called T cells

By recognising and attaching to these two cells, teclistamab forces the cancerous MM cells to come in proximity with the T cells from the body's immune system. This enables the T cells to effectively destroy the MM cancer cells (41). **Figure 2** below provides an overview of how teclistamab works.

Figure 2: How teclistamab works



Abbreviations: BCMA: B cell maturation antigen; CD3: cluster of differentiation 3; IFN-y: Interferon gamma; IL10: interleukin 10; MM: multiple myeloma; TNF-a: tumour necrosis factor – alpha.
Source: Source: Adapted from: Ben-Ari (2022).(42)

Further information on how teclistamab works can be found in the patient information leaflet here: Patient Information Leaflet (Tecvayli, medicines.org.uk) (43).

How is teclistamab different from existing treatment options for TCE RRMM?

As mentioned in **Section 2c**) Current treatment options:, there are no new or effective treatment options available in the UK for patients with TCE RRMM. Patients with TCE RRMM have received treatment from all available standard treatment drug classes for MM at earlier disease stages. In the absence of new therapies, pomalidomide plus low-dose dexamethasone, which is from a drug class received previously (i.e, iMiD), is the predominantly received treatment for these patients. As such, patients with TCE RRMM have poor treatment response rates, resulting in an increased frequency of symptoms experienced, poor HRQoL and short life expectancy (8, 20, 44).

Teclistamab is a **first-in-class** (refers to the first drug which uses a new and unique mechanism of action) treatment with a distinct target of BCMA on MM cancer cells and CD3 receptors on T-cells of the immune system. It has been shown to achieve high rates of complete response, thereby extending overall life expectancy in patients with TCE RRMM (40). Teclistamab therefore offers the potential to provide an effective treatment option from a new drug class for patients with TCE RRMM who otherwise have limited treatment options that can improve their quality of life and overall life expectancy.

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.

Teclistamab is not intended to be used in combination with any other treatments in this patient population.

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 teclistamab taken?

Teclistamab is delivered as an injection by trained medical personnel under the patient's skin (stomach or thigh), known as a **subcutaneous** injection. Teclistamab is available as a 10 mg/mL and 90 mg/mL solution for subcutaneous injection.

How much medicine do patients take and when?

A doctor will determine the **dosage** of teclistamab to be given to patients. This dosage will depend on the patient's body weight and will be given in the form of a **step-up dosing** regimen in the first few days before reaching the 'maintenance dose'. This means that the drug dosage patients receive will increase with each subsequent dose, in line with the recommended dosage listed below:

- First dose received on day 1: 0.06 mg/kg
- Second dose received two to seven days later: 0.3 mg/kg
- Third dose received two to seven days later: 1.5mg/kg

Patients continue to receive doses of 1.5 mg/kg every week, known as maintenance doses which are aimed at maintaining treatment benefit experienced by patients. Patients would continue to receive such doses until the patient's disease progresses or the patient experiences unacceptable toxicity.

- For patients who achieve a complete response on teclistamab (see **Section 3e**) Efficacy for explanation of complete response) for at least six months, the frequency of their dose can be reduced from every week to once every two weeks.

In the first 48 hours of the initial three doses of teclistamab, 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 teclistamab can be found in the patient information leaflet (PIL) here: Patient Information Leaflet (TECVAYLI, medicines.org.uk) (43).

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 Teclistamab in TCE RRMM

The MajesTEC-1 trial (NCT03145181/NCT04557098) has studied teclistamab for the treatment of adult patients (aged ≥ 18 years old) with RRMM who had received treatment from three drug classes which include PI, IMiD, anti-CD38 mAb. It is a first in-human trial for teclistamab in patients with TCE RRMM. The trial was initiated on 16th May 2017, with an estimated completion date of 25th September 2025 (45).

The MajesTEC-1 trial is an international, multicentre, phase 1/2, single-arm, open-label trial. This means that all patients in the trial received teclistamab and that all patients knew

they were receiving teclistamab. The trial was designed as a single-arm trial due to the absence of established standard of care for patients with TCE RRMM. The study took place at various sites situated across the United States, Canada and Europe including locations in the United Kingdom.

The MajesTEC-1 trial looked at how well the MM cells respond to teclistamab (overall response), how teclistamab works to treat TCE RRMM (its efficacy), the most optimal dosing regimen of teclistamab, how tolerable (safe) teclistamab is, as well as its impact on patient HRQoL. Data collected from the MajesTEC-1 trial have been reported in the publication by Moreau *et al.* 2022 and the results from long-term follow-up were presented more recently in the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting by van de Donk *et al.* 2023 (40).

More information about the MajesTEC-1 trial can be found here:

- van de Donk *et al.* 2023 (46) (January 2023 data cut-off, median follow-up of 23 months)
- Moreau *et al.* 2022 (40) (March 2022 data cut-off, median follow-up of 14 months)
- ClinicalTrials.gov (Study Details | A Study of Teclistamab in Participants With Relapsed or Refractory Multiple Myeloma | ClinicalTrials.gov) (45)

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 MajesTEC-1 trial, the efficacy of teclistamab was measured by the following outcomes listed below (46, 47). Data from the MajesTEC-1 trial below are the latest available published data (January 2023 data cut-off) with a median (average) follow-up of ~2 years presented at the 2023 ASCO Annual Meeting by van de Donk *et al.* 2023 (46). There are more up-to-date unpublished data from MajesTEC-1 (August 2023 data cut-off) with a longer median follow-up of >2 years 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 (47). A partial response means that M-protein levels are at least 50% lower than it was before treatment (48). 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 (48).

Achieving a complete response is important for patients as they can expect their remission to last longer and are likely to live longer as a result. In the MajesTEC-1 trial (January

2023 data cut-off), patients had a high ORR of 63.0%, with approximately 45.5% of patients achieving a complete response or better (46). As ORR is linked with OS in RRMM, the high ORR observed in patients receiving teclistamab would typically also correspond to better long-term survival outcomes observed in these patients (49).

Duration of response

Duration of response was measured in the MajesTEC-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 (47). Duration of response is therefore an important readout of how effective the treatment is by assessing how long the treatment response lasts.

In the MajesTEC-1 trial (January 2023 data cut-off), patients who experienced a response recorded a median duration of response of 22 months before having signs of MM reappearing (46). Patients who had achieved a complete response or better had a longer median duration of response of 27 months (46). More than half the patients did not have signs of MM reappearing at the time of the latest published data.

Progression-free survival

Progression-free survival (PFS) was measured in the MajesTEC-1 trial as the time between patients receiving their first dose of teclistamab and having signs that MM has progressed (refers to the worsening of the disease) or death (47). Progression-free survival is an important output to assess treatment effectiveness as it is closely related to overall survival (OS). In the MajesTEC-1 trial (January 2023 data cut-off), patients experienced a median PFS of 11 months, meaning on average, patients went 11.3 months after receiving their first dose of teclistamab before showing signs that their MM had progressed (46). Patients who had achieved a complete response or better had a longer median PFS of 27 months (46).

Overall survival

OS is how long people live after receiving the first dose of treatment. The follow-up data collected from the MajesTEC-1 (January 2023 data cut-off) found that patients had a median OS of 22 months, meaning on average, patients lived for 22 months after receiving their first dose of teclistamab (46). This outcome is a startling contrast to the estimated life expectancy of 7 to 10 months for patients undergoing treatment with pomalidomide with low-dose dexamethasone (9).

At the time of the January 2023 data cut-off, after a follow-up of approximately two years, median OS was not reached in patients who had achieved complete response since the previous data cut-off of March 2022 (46). The latest OS results (August 2023 data cut-off) for patients who achieved a complete response or better are presented in the Company Submission.

Indirect treatment comparison

When there are no data directly comparing two drugs, 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 done for teclistamab from the MajesTEC-1 trial compared with outcomes for pomalidomide plus low-dose dexamethasone from the UK real-world cohort study analysing anonymised data from the National Cancer Registration and Analysis Service (NCRAS) dataset.

The NCRAS is a national database in England which collects data about the diagnosis and treatment of various cancers. There is currently very little research about patients in the UK with TCE RRMM. In this submission, the Company initiated a registry study using the NCRAS database and other linked datasets, thereafter called the UK TCE RRMM cohort study, to analyse routine data on patients with TCE RRMM who received pomalidomide plus low-dose dexamethasone as part of their NHS care. The data from this study were used to compare the effectiveness of teclistamab and pomalidomide plus low-dose dexamethasone.

Statistical methods were used to adjust for any differences in patient characteristics in the MajesTEC-1 trial and UK TCE RRMM cohort study which might impact patient outcomes. This was performed to ensure that comparison of outcomes between teclistamab and pomalidomide plus low-dose dexamethasone remained as fair as possible, with difference in outcomes being due to the treatment received and not due to other factors. This statistical analysis is explained in further detail in the Company Submission.

Outcomes that were investigated in the indirect treatment comparison include:

- 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.
- Time to next treatment (TTNT): This refers to the earliest occurrence of either a change in line of treatment or death within the study period. TTNT was used instead as PFS outcomes were not reported in the NCRAS dataset, and time to next treatment is closely related to PFS, as validated by clinical experts consulted as part of this submission. A longer TTNT indicates that patients have a longer period of therapeutic benefit.

Overall, the results from the ITC demonstrated substantial improvements in TTNT and OS with teclistamab compared to pomalidomide plus low-dose dexamethasone, as assessed through various statistical methods. The results showed that patients receiving teclistamab would live for more than an additional year longer than patients receiving PomDex.

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.
The aforementioned efficacy findings from the MajesTEC-1 trial (data cut-off of January 2023) were presented at the 2023 ASCO Annual Meeting by van de Donk *et al.* 2023 with a median follow-up of approximately 2 years (46). However, the presentation did not include the results concerning the impact of teclistamab on the quality of life of TCE RRMM patients. Therefore, the overall benefits to patients receiving teclistamab are outlined below based on the data reported in Moreau *et al.* 2022, with a data cut-off of March 2022 (40). This included: • Meaningful improvements in symptoms, physical functioning and overall health • Large reductions in pain and fatigue with continued teclistamab treatment • Improvements in severity of disease There are more up-to-date unpublished data from MajesTEC-1 (August 2023 data cut-off) with a longer median follow-up duration of > 2 years in the Company Submission. The updated data from the August 2023 data cut-off are generally supportive of the overall benefit of teclistamab reported from the March 2022 data cut-off mentioned above.

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** and the same medicine can produce different reactions in different people. Evidence for the safety of teclistamab is based on all patients with TCE RRMM who received at least 1 dose of teclistamab in the MajesTEC-1 trial (47).

Very common serious side effects which may affect more than 1 in 10 people receiving teclistamab include (43):

- A serious immune reaction known as **cytokine release syndrome (CRS)** that may cause fever, chills, nausea, headache, fast heartbeat, feeling dizzy, and difficulty breathing
- Low level of antibodies called **immunoglobulins** in the blood (**hypogammaglobulinaemia**), which may make infections more likely
- Low levels of a type of white blood cells (**neutropenia**)
- Infection, which may include fever, chills, shivering, cough, shortness of breath, rapid breathing and rapid pulse

A complete list of all potential side effects associated with teclistamab including rare side effects can be found in the Patient Information Leaflet (TECVAYLI, (medicines.org.uk)) (43).

Managing side-effects

Teclistamab is associated with side effects which include neutropenia, infections and CRS, as experienced by patients in the MajesTEC-1 trial, but the side effects experienced were generally manageable with supportive care provided (46). This was in line with the clinician feedback received as part of the Company submission which indicated that the management of side effects of teclistamab in clinical practice has improved compared to the data in the MajesTEC-1 trial. This is due to the improvements in the management of COVID-19-related infections, increased experience of clinicians in the use of BCMA-targeting bispecific antibodies and switching to a less frequent dosing regimen. As of the January 2023 data cut-off, no new side effects were recorded, indicating that the safety profile of teclistamab is well-characterised and can be easily managed (46).

In order to reduce the risk of side events, in particular CRS, teclistamab is given to patients according to a step-up dosing schedule. Patients are monitored for signs and symptoms of CRS and are advised to remain in close proximity to qualified treatment

facilities for the first 48 hours following the initial three doses of teclistamab. This ensures prompt and effective management of any side effects.

Moreover, for patients who achieve a complete response or better for at least 6 months, the frequency of dose received by patients may be reduced from once a week to once every two weeks. This less frequent dosing regimen is associated with a reduced risk of infections, as supported by the findings from the January 2023 data cut-off of the MajesTEC-1 trial (46, 50). Patients who had switched to a lower dose frequency of once every two weeks experienced half as many grade ≥3 infections than patients who had remained on weekly dosing (46, 50). Details on the management of side effects can be found here in the Summary of Product Characteristics of teclistamab (TECVAYLI, INN-teclistamab (europa.eu)) (51).

Changes in teclistamab dose received

Teclistamab was generally well tolerated by patients in the MajesTEC-1 trial. Side effects resulting in the need for dose reduction or discontinuation were infrequent. At the time of the January 2023 data cut-off, 0.6% of patients had a dose reduction and less than 5% of patients discontinued treatment with teclistamab due to side effects (46).

This is in line with the observations from the data reported in Moreau *et al.* 2022 based on the March 2022 data cut-off whereby 0.6% of patients received a reduction in their teclistamab dose because of side effects, and 1.2% of patients discontinued treatment with teclistamab because of side effects (40). More than half of patients (63%) skipped a dose of teclistamab treatment due to side effects (40). This shows that most patients are able to continue receiving treatment benefit from teclistamab, and are able to manage side effects by skipping a dose, without having to stop treatment due to side effects experienced.

As of the January 2023 data cut-off, a cumulative total of seven treatment-related deaths occurred since the start of the study, including four deaths due to COVID-19 infections (40). However, these deaths are unlikely to represent of current UK clinical practice. The World Health Organisation declared the novel coronavirus outbreak as a global pandemic on the 11th March 2020, and the MajesTEC-1 trial started six months later, at a time when deaths due to COVID-19 were high (52). As COVID-19 is now much more effectively managed in current clinical practice and COVID-19 vaccines are widely available, it is anticipated that any deaths due to COVID-19 in current clinical practice would be much lower compared to the MajesTEC-1 trial.

3h) Summary of key benefits of treatment for patients

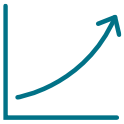
Issues to consider in your response:

- 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

Patients with TCE RRMM have been exposed to all three standard drug classes given to patients with MM in the UK. Their chances of responding positively to current treatments such as pomalidomide plus low-dose dexamethasone is therefore limited given their prior exposure to the same drug class. This gives rise to an expanding population of TCE RRMM patients enduring high symptomatic burden, diminished HRQoL and poor clinical outcomes characterised by a notably short life expectancy (9).

The rapidly evolving treatment landscape in MM underscores the inevitably and equally critical need for effective treatments from a novel drug class, exemplified by teclistamab. The key benefits of teclistamab to patients with TCE RRMM include:

Novel mechanism of action: Teclistamab is a first-in-class treatment, used on its own, which has a distinct target of BCMA on MM cancer cells and CD3 receptors on T-cells of the immune system. This removes the need to re-use a treatment from the same drug class as a patient has already received. Moreover, teclistamab is an off-the-shelf BCMA therapy which means that patients can receive teclistamab immediately without waiting, thereby receiving timely treatment ahead of further disease progression.



Longer life expectancy: Treatment with teclistamab yields deep and sustained response rates for patients with TCE RRMM. This positive response is often associated with improved OS rates, suggesting that a higher response rate typically corresponds to improved long-term survival outcomes. Based on the most recent data cut-off, teclistamab substantially prolongs the overall life expectancy for patients with TCE RRMM by more than a year, in stark contrast to those receiving pomalidomide plus low-dose dexamethasone in the latest data cut-off of the UK TCE RRMM cohort study based on NCRAS data, who face a shorter life expectancy of less than 10 months (ranging from 7 to 10 months) (9).

Well understood and tolerated safety profile: Teclistamab has a tolerable safety profile whereby the majority of patients are able to continue receiving treatment benefit for a prolonged duration. Side effects are well understood with no new side effects observed in the latest data cut-off of the MajesTEC-1 trial.

To minimise the risk of side effects, it is recommended to follow a dosing regimen that increases in intensity when starting treatment. Once the maintenance dose is reached and as long as patients are getting benefit from teclistamab, the dosing frequency may be reduced from once a week to every 2 weeks for those who have achieved CR or better for at least six months. Since teclistamab does not require continuous administration of steroids (such as dexamethasone), patients avoid experiencing side effects commonly associated with steroids which can negatively impact patients'

HRQoL. Routine supportive care measures can be implemented to manage any side effects observed.

Improved patients' and carers' HRQoL: Teclistamab provides meaningful improvements in both overall and MM-specific QoL burden for patients with TCE RRMM. This is achieved by providing an effective treatment option that reduces the impact of the pain and fatigue symptoms experienced. TCE RRMM and its treatment not only impacts the quality of life of patients but also that of their caregivers and support networks. As mentioned in **Section 2a**) The condition – clinical presentation and impact, caregivers often experience a high burden relating to providing direct care and providing emotional support to the person with TCE RRMM they are caring for. The benefits associated with teclistamab treatment are therefore also likely to extend to caregivers, due to the improvements in disease outcomes translating to a decreased level of care required.

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, teclistamab may not work for everyone and therefore some patients may not respond to treatment. However, the results of the MajesTEC-1 trial showed that almost 2 in 3 patients responded to treatment with teclistamab, and for these patients, treatment resulted in substantially improved PFS and OS when compared with pomalidomide plus low-dose dexamethasone, as mentioned in the results from the ITC described in **Section**

3e) Efficacy .

Side effects

In a small proportion of patients, treatment with teclistamab can result in potentially life-threatening side effects, such as CRS (51). CRS is a serious immune reaction with symptoms such as fever, chills, nausea, headache, fast heartbeat, dizziness or difficulty breathing (43). Teclistamab can also cause side effects such as neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) which is a

serious immune reaction which affects the nervous system. However, in the MajesTEC-1 trial, ICANS was very rarely experienced (43).

In order to reduce the risk and impact of CRS, teclistamab is given to patients according to a dosing schedule which increases in intensity, as mentioned in **Section 3c**) Administration and dosing. Pre-treatment medication such as **corticosteroids** (this refers to medicine that reduce inflammation, [i.e. swelling]), **antihistamines** (this refers to medicine that treat allergy symptoms) and **antipyretics** (this refers to medicine that reduce fever) that are also given one to three hours before each treatment dosage to reduce the risk of CRS (43). Teclistamab is required to be given in a hospital setting under the supervision of healthcare professionals who are experienced in the treatment of MM (43). These hospitals and healthcare professionals would be equipped with appropriate medical equipment and trained to promptly manage severe reactions, such as CRS and ICANS (43).

Administration

Teclistamab should be taken for as long as the patient continues to receive clinical benefit. Hence, patients would make weekly visits to the hospital to receive their maintenance dose of teclistamab from a trained healthcare professional. However, if patients continue to receive benefit from teclistamab use (i.e., a 'complete response') for at least six months, patients may receive injections once every two weeks instead, thereby minimising the burden associated with weekly clinical visits. Moreover, these patients would be seen in outpatient facilities which means there is no requirement for overnight hospital stays unlike the initial rounds of receiving teclistamab.

3i) 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.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to

existing medicines. To assess this, they will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the **health economic model** to perform an analysis, which compares the costs and benefits of the new treatment (teclistamab) with the existing treatment option (pomalidomide plus low-dose dexamethasone) over the lifetime of patients with TCE RRMM.

How the model reflects TCE RRMM

The economic model was designed to reflect the key features of TCE RRMM and **clinical practice** in the UK. To do this, a model structure called a **partitioned survival model** was chosen, as this tool is commonly used to model cancer treatments. The model was used to predict future survival outcomes of patients with TCE RRMM (based on survival equations) and compares teclistamab with the existing treatment option (pomalidomide plus low-dose dexamethasone). The economic model consists of three health states, with "progression free" being the best health state:

- Progression free: the patient's disease is responding to the treatment and not actively progressing to more advanced stages
- Progressed: the patient's cancer has worsened
- Death

Modelling how much teclistamab improves overall survival and progression-free survival

The results from the MajesTEC-1 trial for teclistamab and data from the UK TCE RRMM cohort study for pomalidomide plus low-dose dexamethasone respectively were used to inform the economic model. The main results from these studies used in the model were overall survival and progression-free survival. In the absence of PFS data in the UK TCE RRMM cohort study, TTNT was used as a proxy (see **Section**

3e) Efficacy). OS and PFS were the main results used in the model because they were considered relevant to what would be considered as successful survival outcomes when treating TCE RRMM in clinical practice in the UK. Additional outcomes such as response and duration of response were not explicitly included in the model.

The results from the most recent data cut-off of the MajesTEC-1 trial (currently unpublished) were used to inform the model. However, the economic model simulates patients for the rest of their lifetime, a much longer period of time than the length of the trial. Data for teclistamab and pomalidomide plus low-dose dexamethasone were used to predict how long people treated with teclistamab or PomDex in UK clinical practice would remain progression free and how long they would live (see **Section**

3e) Efficacy for details of the indirect treatment comparison).

Modelling how much teclistamab improves quality of life

Quality-of-life data in the model was based on data observed in the MajesTEC-1 trial. In this study, quality of life 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 trial converted the quality-of-life measurements collected from questionnaires into health utility inputs to inform the economic model. The MajesTEC-1 trial represented the best source of quality-of-life data to inform the model given it is in the patient population of interest and included patients receiving treatment with teclistamab.

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model to account for differences between the costs of teclistamab and pomalidomide plus low-dose dexamethasone. These costs 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
- The cost of subsequent treatment(s), including end-of-life treatments

Uncertainty

- Although the most recent data from the trial was used in the model, there is uncertainty in how long people would remain alive for each treatment as data are only available for a certain duration of follow-up and therefore predictions need to be used to inform decision-making
- Alternative assumptions have been tested in the model and the impact on the results presented in Document B

Cost effectiveness results

One of the main outcomes of an economic model is the quality-adjusted life years (QALYs) of the patients receiving treatment. This reflects how long the patients survive with treatment adjusted to account for quality of life. For example, one year of survival with low quality of life equals to less than one QALY. The resulting accumulation of costs and QALYs associated with each treatment, and the ratio between these values, indicates whether the treatments are cost effective or not. A ratio of £20,000 to £30,000 per QALY is considered cost-effective for a new treatment to be adopted by the NHS.

Overall, the results of the economic analysis showed that teclistamab was cost-effective versus PomDex at a ratio of £20,000 to £30,000 per QALY, when teclistamab is associated with a confidential discount price. Pomalidomide is also associated with a confidential discount price, but because this is confidential it could not be included in the economic analysis.

It is important to note that the Company's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions that are different from the assumptions that the company used in their model. In addition, some comparators treatments may have confidential discounts that the Company do not have access to.

Benefits of teclistamab not captured in the economic analysis

Treatment with teclistamab 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. For example, patients with TCE RRMM experience significant symptomatic burden coupled with high levels of emotional distress due to the lack of novel treatment options (14). In addition, the benefit of an increased level or duration of response for patients at this stage of the pathway are not explicitly captured. Teclistamab offers the hope of a new treatment option which offers benefits in improved response rates and extended life expectancy, the value of which is not fully captured in the economic analysis.

Conclusion

The key patient and clinical benefits outlined in **Section 3h**) Summary of key benefits of treatment for patients alongside the findings from the economic analysis indicate that teclistamab represents good value for money and a good use of NHS resources as a novel treatment for patients with TCE RRMM.

3j) 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)

Teclistamab is an innovative treatment which would represent an important advancement in the treatment of TCE RRMM

As mentioned in **Section 3a**) How does the new treatment work?, the exhaustion of all 3 main classes of anticancer treatments accessible to patients with TCE RRMM is anticipated to exacerbate the condition of this patient group. This worsening state is associated with diminished HRQoL and a shorter life expectancy given the existing treatment options in the RRMM treatment pathway. The impact of TCE RRMM extends to both patients and caregivers, affecting their mental and emotional well-being and quality of life. Exposure to multiple rounds of treatment without favourable responses can significantly debilitate patients, stemming from both disease progression and treatment-related effects. Consequently, there is an urgent need for innovative and effective therapies for this patient cohort and those who are involved in their care.

Teclistamab offers a new treatment option, one that is first of its drug class, for patients who have otherwise been exposed to all three available drug classes in the UK. Thanks to its novel mechanism of action, teclistamab facilitates responses which are able to be maintained in heavily pre-treated patients with TCE RRMM, which translate to significant improvements in patient HRQoL, progression-free survival and overall life expectancy. Therefore, a positive recommendation of teclistamab by NICE would represent a step-change in the management of TCE RRMM since the last introduction of anti-CD38 mAbs over five years ago (53, 54). The recommendation of teclistamab would offer hope for a novel and effective treatment in a group of patients who would have otherwise exhausted all treatment options and have very poor prognosis with current treatment.

Finally, the use of teclistamab for patients with TCE RRMM in the UK is expected to foster innovation in the treatment of this patient group, paving the way for future novel treatment options. The treatment pathway for TCE RRMM is undergoing rapid evolution, with numerous ongoing trials exploring innovative therapies and their potential benefits in heavily pre-treated patients (55). The introduction of teclistamab could mean that patients who respond to the treatment may have the opportunity to survive long enough to derive further benefits from upcoming novel treatments as they become accessible in the UK.

3k) 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 teclistamab 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: Understanding myeloma | what is myeloma?: https://www.myeloma.org.uk/understanding-myeloma/what-is-myeloma

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: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

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 reduced number of red blood cells and can 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 (56)
Anti-CD38 monoclonal antibody (anti-CD38 mAb)	An antibody which binds to a protein called CD38 which is found on some blood cell types and in high levels on some cancer cells which includes MM cells (56)
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 expressed on the surface of cancerous plasma cells
Biopsy	A process in which a very small part of tissue in the body is removed to look for signs of disease (57)
Bone marrow	The spongy material found inside the centre of large bones in the body, where all blood cells are made (3)
Clinical outcomes	A measurable change in symptoms, health, quality of life or survival resulting from care given to patients
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 (56). 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 (48)
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 (56)
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
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 these work, what these 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
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial**
European Medicines Agency	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 quality of life 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
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 quality of life in terms of physical and mental health, and vice versa
Health utility inputs	A measure of the preference or value that an individual or society gives a particular health state. This is generally a number between 0 (representing death) and 1 (representing perfect health)
Hypercalcemia	This refers to higher than normal levels of calcium in the blood (56). This is a potential risk associated with advanced cancer
Hypogammaglobulinaemia	This refers to a condition whereby the level of immunoglobulins, otherwise known as antibodies, in the blood is low and risk of infection is high (56)
Imaging	A process that makes pictures of areas inside the body. Imaging uses methods such as x-rays (high-energy radiation), ultrasound

	(high-energy sound waves), and radio waves (56)
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 (56)
Immunomodulatory agent (IMiD)	A substance that simulates or suppresses the immune system and helps the body fight cancer, infection or other diseases (56)
Immunotherapy	A type of therapy that uses immunomodulatory agents (56)
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
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 (56)
Magnetic resonance imaging (MRI)	A procedure which uses radio waves, a powerful magnet and compute 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
Mechanism of action (MoA)	This refers to the process by which a drug works to produce an effect in the body
Medicines and Healthcare products Regulatory Agency (MRHA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom
Multiple myeloma (MM)	MM is a rare and incurable cancer of the **plasma cells**, a type of white blood cell that is found in the **bone marrow**
National Cancer Registration and Analysis Service (NCRAS)	The NCRAS is a national database in England which collects data about the diagnosis and treatment of various cancers
Neutropenia	This refers to a condition whereby a person has a low number of white blood cells called neutrophils. With low levels of neutrophils, a person's immune system is weakened, making it difficult to fight infections (58)
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 achieved partial response or better which is measured by the amount of M-proteins, a type of protein made my MM cancer cells
Overall survival (OS)	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 1	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 2	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 (56)
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 (56)
Progressed	This refers to the worsening of disease
Progression-free	The patient's disease is responding to the treatment and not actively worsening
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 (56)
Proteasome inhibitor (PI)	These are drugs which stop the cell from breaking down any excess proteins within the cell, resulting in cell death
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair
Quality of life (QoL)	This refers to the overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living
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
Relapsed	The return of a disease or the signs and symptoms of a disease after a period of improvement (56)
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 (7). 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

Renal failure	This refers to a condition whereby the kidneys stop working and are not able to remove waste and extra water from blood or keep body chemicals in balance
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 (56)
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

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 (41)
Time to next treatment (TTNT)	Time from the first dose of treatment received until the start of subsequent treatment
Triple-class exposed (TCE)	MM patients who have been given a proteasome inhibitor, immunomodulatory agent and an anti-CD38 monoclonal antibody as 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 (56)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID6333_Teclistamab_ClarificationLetter_[CON].docx	1.0	Yes	13 March 2024

Notes for external assessment groups (EAGs) and NICE

[TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Note: Correction to company base case

Separate to the Clarification Question responses, Janssen have identified a minor error in the cost-effectiveness model, which means that the relative dose intensity of teclistamab was overestimated in the economic model submitted in the Company submission (CS).

ICERs and scenarios provided below as part of the Clarification Question response include the corrected value for the relative dose intensity. A revised copy of the company economic model including the corrected value is also enclosed with the company response. Please see Appendix A for further details regarding the correction and Appendix B for the updated base case results.

Section A: Clarification on effectiveness data

A1. Please clarify why the UK RW TCE RRMM cohort study was not identified by the company SLR.

At the time of the latest update of the Company SLR (31st October 2023), the only publication on the UK RW TCE cohort study was the publication by Elsada *et al.* (2021).[1] The Elsada *et al.* (2021) publication was identified in the company SLR, however it was excluded in error during the title and abstract screen.

Whilst the Elsada et al. publication was excluded from the company SLR, Janssen are confident that the UK RW TCE cohort study, with the extended follow-up period of 23 months presented in the CS, is the best source of evidence for PomDex in this decision problem. As described in Section B.2.9 (page 92) of the CS, the UK RW TCE cohort study collected real-world data on the specific population of interest in the UK and therefore is fully aligned with the population of patients receiving PomDex in UK clinical practice. Additionally, UK clinical experts confirmed that, to their knowledge, the UK RW TCE cohort study is the best available source of data of TCE patients in UK clinical practice.[2] Furthermore, the use of the UK RW TCE cohort study to provide comparative efficacy evidence for PomDex in patients with TCE RRMM was previously accepted in the cilta-cel appraisal and deemed generalisable to UK patients.[3]

A2. Please clarify whether the MajesTEC-1 trial is still recruiting patients with TCE RRMM and, if so, please clarify to which patient cohorts and when enrolment is expected to stop.

Enrolment into all cohorts of the MajesTEC-1 trial was completed on 13th August 2021. No further enrolment for patients with TCE RRRM in any of the cohorts included in MajesTEC-1 is expected.

A2. Please explain how the MajesTEC-1 trial August 2023 data cut median follow-up (30.4 months) was calculated.

Median follow-up for the MajesTEC-1 August 2023 data cut was calculated using the reverse Kaplan-Meier methodology, which is constructed by reversing censoring and death events.[4]

A3. Please provide MajesTEC-1 trial i) OS and ii) PFS median follow-up from each data-cut, using reverse Kaplan-Meier methodology.

Median follow-up for each data cut-off for overall survival (OS) presented in Table 13 in Section B.2.6 of the CS (page 66) were derived using the reverse Kaplan-Meier methodology. However, for completeness, median follow-up for OS for each data-cut off have been reproduced in Table 1 below. Median follow-up for PFS for each data-cut off derived via reverse Kaplan-Meier methodology is provided in Table 1.

Table 1: OS median follow-up for each data cut-off of MajesTEC-1 (months)

Data cut-off	OS median follow-up (95% CI)
September 2021	7.2 [redacted]

March 2022	14.1 [redacted]
January 2023	[redacted]
August 2023 ([redacted] DCO)	30.4 ([redacted])

Abbreviations: DCO: data cut-off; OS: overall survival; PFS: progression-free survival.

Table 2: PFS median follow-up for each data cut-off of MajesTEC-1 (months)

Data cut-off	PFS median follow- up (95% CI)
September 2021	[redacted]
March 2022	[redacted]
January 2023	[redacted]
August 2023 ([redacted] DCO)	[redacted]

Abbreviations: DCO: data cut-off; OS: overall survival; PFS: progression-free survival.

A4. Please clarify how many patients, if any, in the MajesTEC-1 trial phase 1 RP2D cohort (N=40) had previously received treatment with an anti-BCMA treatment.

As outlined in the Section 4.2 (page 80) of the MajesTEC-1 trial protocol, patients who had received prior anti-B-cell maturation antigen (anti-BCMA) therapy were excluded from Phase I and Cohorts A and B of the Phase II portion of the MajesTEC-1 trial.[5] Therefore, no patients in Phase I of the MajesTEC-1 trial had received prior anti-BCMA treatment.

A5. For the base-case and all sensitivity indirect treatment comparisons, please provide the effective sample sizes for the MajesTEC-1 teclistamab arm and the UK RWE TCE RRMM PomDex cohort.

Effective sample sizes (ESS) for the MajesTEC-1 and UK RW TCE cohorts used in the base case and all sensitivity analyses for the indirect treatment comparison (ITC) are provided in Table 3 below. Average treatment effect for the control (ATC) was utilised in the base case analysis, whilst average treatment effect on the treated (ATT), average treatment effect (ATE) and average treatment effect on the overlap population (ATO) were explored as sensitivity analyses.

In the ATT analyses, individual patients in the UK RW TCE cohort were reweighted to ensure the populations aggregate baseline characteristics were more closely aligned to the baseline characteristics of patients in the MajesTEC-1 trial. As such, the ESS of the teclistamab cohort for these sensitivity analyses remain unchanged compared to the unadjusted analyses (Table 3). In contrast, for the ATC analyses, individual patients in the MajesTEC-1 cohort were reweighted to align the aggregate baseline characteristics more closely with those of the UK RW TCE cohort. As such, the ESS of the PomDex cohort for these sensitivity analyses remain unchanged compared to the unadjusted analyses (Table 3).

As noted in Section B.2.9.1 of Document B (page 96), the ATC approach was considered to be the most appropriate methodology for baseline adjustment, as clinical experts noted that the UK RW TCE cohort study provides the best available real-world data on a UK TCE RRMM population receiving PomDex after three prior therapies. This is directly aligned with the population of patients who are anticipated to receive teclistamab in UK clinical practice.

Furthermore, adjusting for five out of the six available covariates was considered the most suitable approach as adjusting for six variables resulted in three of the six variables having standard mean differences (SMDs) above the threshold of 0.2, indicating that differences

persisted between the MajesTEC-1 and UK RW TCE cohorts post-adjustment. The adjustment for five variables resulted in a notable improvement in overlap between the two populations and was therefore considered the most appropriate approach for the base case analysis. Furthermore, UK clinical experts indicated ASCT as one of the lowest priority prognostic variables and that age is highly correlated with prior autologous stem cell transplant (ASCT) status, thereby meaning that adjustment for age also implicitly adjusted for prior ASCT, further highlighting the appropriateness of the 5-variable adjustment process.[2]

Table 3: Effective sample sizes for the base case and all ITC sensitivity analyses

	Teclistamab	PomDex (ECOG 0/1 cohort)
Base case analysis		
Unadjusted	165	645
Adjusted: ATC 5 variables	[redacted]	645
Sensitivity analyses		
ATC 6 variables	[redacted]	645
ATT 5 variables	165	[redacted]
ATT 6 variables	165	[redacted]
ATO 5 variables	[redacted]	[redacted]
ATO 6 variables	[redacted]	[redacted]
ATE 5 variables	[redacted]	[redacted]
ATE 6 variables	[redacted]	[redacted]

Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATO: average treatment effect on the overlap population; ATT: average effect of the treatment; ITC: indirect treatment comparison; PomDex: pomalidomide plus dexamethasone.

A6. Please assess the validity of the proportional hazards assumption for the base case i) OS and ii) PFS (TTNT as a proxy) indirect treatment comparisons.

During the clarification call held between Janssen and the EAG on 29th February 2024, the EAG acknowledged that the requested results of the proportional hazard tests for the base case ITCs had been located in Appendix N of the CS. As such, the results of the proportional hazard tests have not been provided as part of the clarification question response.

On the clarification call, the EAG confirmed that they were seeking further clarification on whether the proportional hazard tests were performed on the adjusted (weighted) or unadjusted data. Janssen would like to clarify that the proportional hazard tests were performed on the base case ITC results e.g. on the **unadjusted** PFS and OS data for PomDex (UK RW TCE Cohort study) and the **adjusted** (weighted) (sATC [n=5 variables]) PFS and OS data for teclistamab, (sATC (n=5 variables), as indicated in the accompanying figure captions (Figure 15−Figure 25, page 430−436) in the CS.

A7. CS, Table 27 shows the SMDs before and after the 5-variable adjustment. Please clarify why prior ASCT is included in this table and explain why the number of

patients who received prior ASCT in the teclistamab arm changes by n=1 after 5-variable adjustment.

As noted in response to clarification question A5, in the ATC 5-variable adjustment process, individual patients in the MajesTEC-1 trial were assigned different weights to align the aggregate baseline characteristics of the trial population more closely to those in the UK RW TCE cohort study. During the adjustment process, individual patients in the MajesTEC-1 trial whose baseline characteristics were more closely aligned to patients in the UK RW TCE cohort study (with respect to the 5 variables adjusted for) received higher weights. Higher weighting of these patients resulted in an apparent increase in the proportion of patients (and therefore the number of patients) with a given characteristic in the MajesTEC-1 trial (and vice versa for patients given lower weights).

Whilst ASCT was not included in the base case adjustment, the distribution of prior transplant is indirectly influenced by the weights each patient receives in the base case adjustment. Patients who were upweighted owing to the adjustment of other covariates, such as Eastern Cooperative Oncology Group (ECOG) status and age, may have received prior ASCT, thereby resulting in an apparent increase in the number of patients receiving prior ASCT post-adjustment. Prior ASCT was therefore retained in Section B.2.9.3 (page 103); Table 27 of the Company submission to reflect differences in this variable, pre- and post-adjustment.

Section B: Clarification on cost effectiveness data

B1. Please generate **teclistamab TTD** estimates by attenuating chosen parametric distributions to align with the midpoint of clinical expert 5, 10 and 15 year teclistamab TTD estimates and provide scenario analysis results generated by using the upper and lower limits suggested by clinical experts.

During the clarification call, the EAG indicated that questions B1 and B2 were raised to obtain estimates of interest for teclistamab and PomDex using a consistent attenuation method across all outcomes. While Janssen recognizes the importance of exploring uncertainty, we want to emphasize the value of data-driven extrapolation. It is crucial to rely on actual data rather than solely on clinical expert opinion, as this aligns with NICE's hierarchy of evidence. Robust data with long follow-up is available for both PomDex and teclistamab across all endpoints. Janssen acknowledges, however, that there is greater uncertainty surrounding the long-term PFS and OS outcomes for teclistamab. To ensure external validity in the face of this uncertainty, a conservative approach was taken by attenuating these estimates using input from clinical experts. Overall, Janssen believes that a combination of data-driven extrapolation and input from clinical experts provides a robust approach for estimating outcomes in the base case analysis.

Janssen would like to reiterate the point that the approach selected for TTD estimates in the base case analysis is preferable due to the clinical plausibility of the original TTD extrapolations. As such, unlike with PFS and OS, Janssen consider no attenuation for teclistamab TTD is necessary on the chosen parametric distribution.

As requested, additional scenarios using a consistent attenuation method incorporating explicitly long term teclistamab TTD estimates are provided in Table 4 below. To generate these scenarios, the chosen parametric distribution for TTD (Gamma) was attenuated using the midpoint of the clinician estimates and the combined impact of this adjustment along with the base case teclistamab OS and PFS outcomes (using TTNT as a proxy) is presented in scenario 1. Additionally, scenarios 2 and 3 present the impact of selecting the upper and lower bounds of the clinician estimates for OS, PFS and TTD. However, it should be noted that these additional scenarios are also deemed less plausible as they reflect the extremes of the clinical estimates elicited.

As noted above, all results presented below include the corrected % of teclistamab missing doses (see Appendix A for further details).

Table 4. Teclistamab TTD attenuation scenario analysis results for teclistamab versus PomDex (deterministic; TEC PAS price, 1.2x severity modifier applied)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
1	Teclistamab OS, PFS and TTD attenuated to clinician estimate midpoint	[redacted]	[redacted]	[redacted]	[redacted]	£3,441	0.00	-0.11
2	Teclistamab OS, PFS and TTD attenuated to upper bound of clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	£6,149	0.24	0.04
3	Teclistamab OS, PFS and TTD attenuated to lower bound of clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	£443	-0.27	-0.28

Abbreviations: INHB: incremental net health benefit; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

B2. Please generate **PomDex OS and PFS** estimates by attenuating chosen parametric distributions to align with the midpoint of clinical expert 5, 10 and 15 year PomDex OS and PFS estimates and provide scenario analysis results generated by using the upper and lower limits suggested by clinical experts.

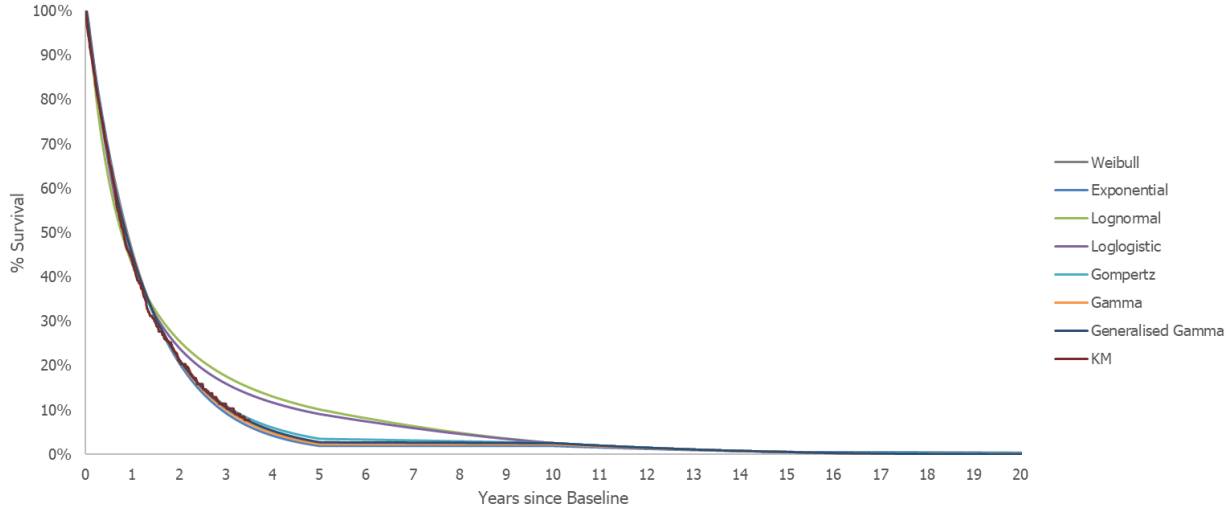
The requested scenario can be found in Table 5 below.

As noted in response to B1, Janssen consider that where possible a data driven approach to extrapolation should be taken with clinical expert estimates used for validation rather than explicitly used in extrapolation. As such, Janssen emphasise that, due to the maturity of the data from the UK RW TCE cohort study, the use of attenuation for the PomDex arm is not appropriate in the base case. Overall, there is less uncertainty in the PomDex OS as there were 464 observed OS events (71.9%) of the overall PomDex cohort.

In the CS, because of the greater uncertainty in the teclistamab OS and PFS extrapolations (compared to TTD for teclistamab and PFS/OS for PomDex), Janssen conservatively implemented an additional attenuation using clinical estimates. This was appropriate in the absence of survival curves which fitted the observed data and aligned with clinical estimates at the same time. However, for PomDex, the data and number of OS events observed over the long follow-up period of 23 months provide greater certainty in extrapolating the observed OS and PFS (TTNT as a proxy). Consequently, there is no need for additional attenuation based on clinical feedback. This is clearly illustrated in Figure 1 and Figure 2 below, where the OS and PFS (i.e. TTNT as proxy) long-term extrapolations of all the parametric distributions overlap with each other (excluding the log-logistic and log-normal distributions as they are implausible given the observed KM data).

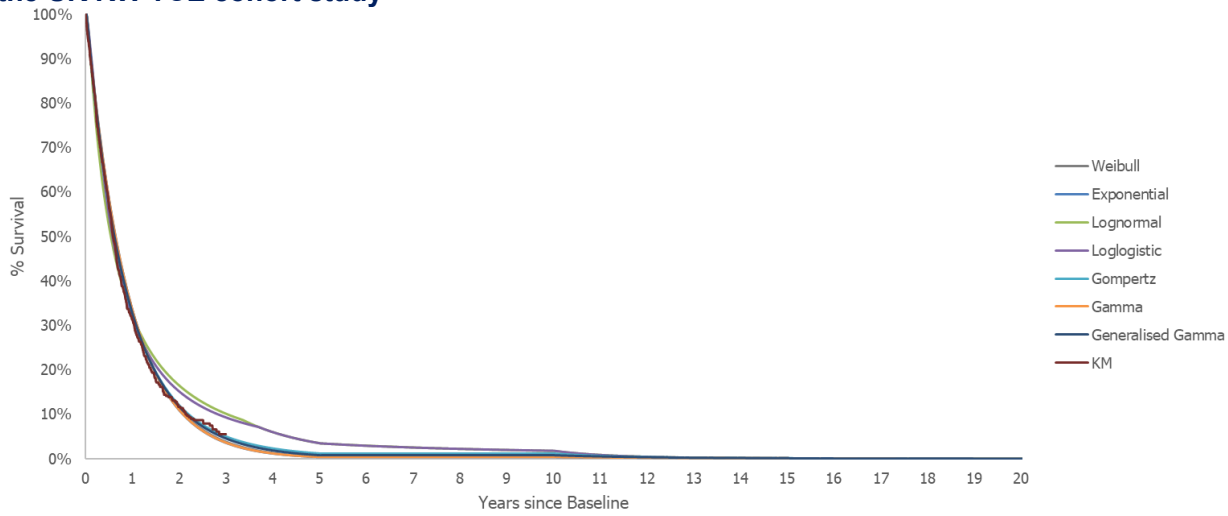
Furthermore, upon analysing the PomDex OS hazard rate over time, it becomes apparent that the approach which uses clinical estimates to attenuate the long-term PomDex extrapolations leads to sudden and implausible decreases (84% reduction in the weekly hazard) in hazard risk at the time when the adjustment starts (as shown in Figure 3). This is subsequently followed by a sudden increase in the OS hazard at year 10. This stands in stark contrast to the smoother plot observed when using the unadjusted extrapolation for PomDex OS (see Figure 4).

Figure 1. Extrapolation of attenuated OS for PomDex using IPD from the UK RW TCE cohort study



Abbreviations: IPD: individual patient data; OS: overall survival; UK: United Kingdom

Figure 2. Extrapolation of attenuated PFS (as proxy for TTNT) for PomDex using IPD from the UK RW TCE cohort study



Abbreviations: IPD: individual patient data; PFS: progression-free survival; UK: United Kingdom

Figure 3.OS Hazard rate over time for PomDex when attenuated long-term extrapolations

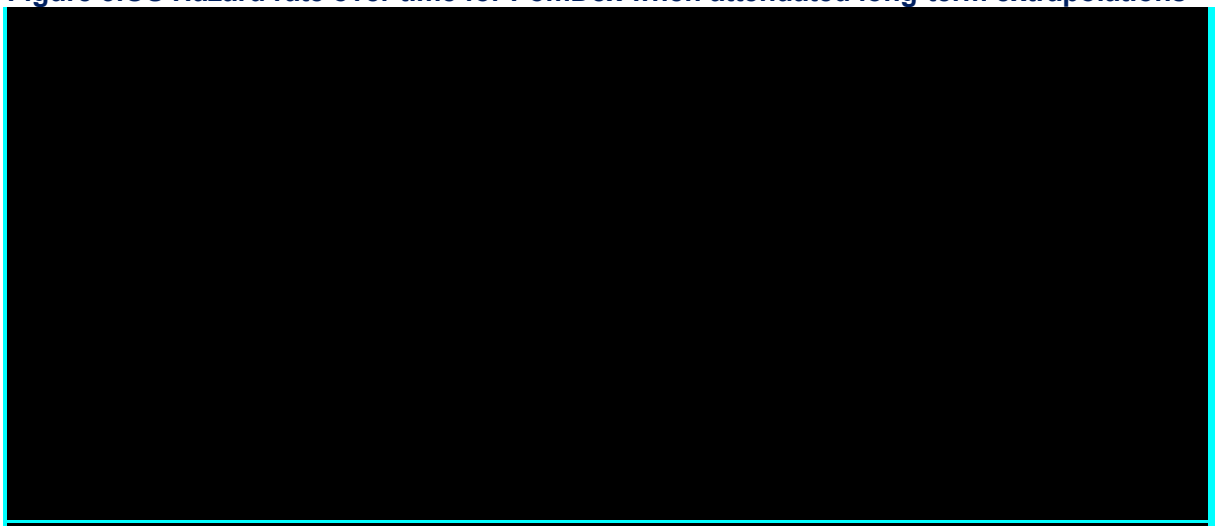


Figure 4. OS Hazard rate over time for PomDex when using unadjusted long-term extrapolations

Table 5. PomDex attenuation scenario analysis results for teclistamab versus PomDex (deterministic; TEC PAS price, 1.2x severity modifier applied)

Scenario		Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case		[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
1	PomDex OS, PFS, TTD and Teclistamab OS and PFS attenuated to clinician estimates midpoint	[redacted]	[redacted]	[redacted]	[redacted]	-£517	-0.07	-0.05
2	PomDex OS, PFS, TTD and Teclistamab OS and PFS attenuated to upper bound of clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	-£359	0.14	0.15
3	PomDex OS, PFS, TTD and Teclistamab OS and PFS attenuated to lower bound of clinician estimates	[redacted]	[redacted]	[redacted]	[redacted]	-£577	-0.26	-0.24

Abbreviations: INHB: incremental net health benefit; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

B3. Please justify why, at baseline, PFS utility for patients treated with PomDex is lower than PFS utility for patients treated with teclistamab.

As described in Section B.3.4.5 of the CS (page 155 and 156), the baseline PFS utility differed for the PomDex and teclistamab arms because health state utility values (HSUVs) for PFS were derived from the MajesTEC-1 and MM-003 trials for teclistamab and PomDex, respectively. PFS HSUVs for PomDex were derived from the MM-003 trial as no utility data were available from the UK RW Are TCE cohort study.

To explore the impact of this, a scenario analysis was conducted in which the PFS HSUV for PomDex was set equal to the baseline utility value for teclistamab ([redacted]). This scenario analysis included a correction to the relative dose intensity (RDI) for teclistamab, further details of which are provided in 8. Jesus FSM, Katja CW, Kevin WS, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica 2015;100:1334-1339.

Appendix A: Correction to teclistamab relative dose intensity. The results of this scenario analysis are provided in Table 6

Table 6 below and demonstrate that setting the baseline utility values equal between arms had a negligible impact on the base case INHB, resulting in a change of [redacted].

These results therefore provide confidence that the base case ICER is robust to uncertainty surrounding the baseline PFS HSUVs used between cohorts.

Table 6: Scenario analysis in which baseline PF HSUVs is set as equal between the teclistamab and PomDex arms (deterministic; TEC PAS price, 1.2x severity modifier applied)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Baseline PF HSUVs set equal between arms	[redacted]	[redacted]	[redacted]	[redacted]	£0	-0.04	-0.04

Abbreviations: HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; N/A: not applicable; PF: progression-free; QALY: quality-adjusted life year.

B4. IG use varies between UK clinical practice (IV: [redacted]; SC: [redacted] and the MajesTEC-1 trial (IV: [redacted]; SC: [redacted] in the CS, it is stated that differences in IG use may potentially impact safety and efficacy outcomes (CS, p164). In scenario 10a, IG costs are excluded and in scenario 10b, UK usage rates have been used; results from these scenarios only affect costs, not QALYs. Please provide results from scenario 10a and scenario 10b that, in addition to exploring the effect of varying IG use on costs, also explore the effect of varying IG use on safety and efficacy outcomes.

Janssen acknowledges the EAG's request to explore the effect of varying Ig use on safety and efficacy outcomes, however considers that currently there is insufficient evidence to robustly quantify this effect. Janssen also considers that quantifying this impact in a robust manner represents answering a fundamentally different decision problem i.e., evaluating the cost effectiveness of teclistamab in combination with varying doses of Ig, which requires in itself an evaluation of the cost effectiveness of the UK clinical policy of Ig.

Janssen maintains that the evidence presented in the base case (i.e., where efficacy/safety results and Ig usage are both directly reflective of MajesTEC-1 data) represents the most relevant evidence for decision making as it directly addresses the decision problem. At the same time, Janssen recognises that the Ig use in the MajesTEC-1 trial exceeds the indications currently listed in the commissioning policy for therapeutic immunoglobulin in the UK.

In response to clarification question B4, Janssen has provided exploratory results from scenario 10a (Ig costs excluded) and scenario 10b (UK Ig usage rates in MajesTEC-1) whereby the effect of varying IG use on outcomes has been explored (in addition to the effect of varying Ig use on costs provided in the CS) based on clinical opinion and arbitrary adjustments to the QALY and/or AE related disutility in the teclistamab arm to provide reassurance to the EAG of the impact on the base case INHB. This is summarised in Table 7 below.

Further, Janssen considers it crucial that when contextualising MajesTEC-1 results to UK clinical practice, any potential impact of Ig on observed outcomes (e.g., reduced Ig use in UK clinical practice vs MajesTEC-1 potentially adversely impacting teclistamab outcomes) should be considered in the wider context of the impact of COVID (i.e., teclistamab outcomes likely better in UK clinical practice post-peak COVID era vs MajesTEC-1), which is likely to have a larger impact on outcomes than any differences in Ig use between MajesTEC-1 and UK clinical practice.

For the scenarios presented in Table 7, two approaches to quantifying the potential impact of no/reduced Ig use on outcomes have been provided – these are described below.

1) QALY decrement applied to the teclistamab arm

- ***a.*** **Scenario 10a (No Ig included)**: An illustrative QALY decrement of 5% was applied to the teclistamab arm to capture the potential impact of **no usage** of Ig on outcomes. This results in an [redacted] change in the INHB from the base case analysis.
- ***b.*** **Scenario 10b (IV: [redacted]; SC: [redacted]):** An illustrative QALY decrement of 2% was applied to the teclistamab arm to capture the potential impact of **reduced Ig use** (per UK

clinical practice) on outcomes. This results in an [redacted] change in the INHB from the base case analysis. Given a 5% QALY decrement was applied in Scenario 10a in which *no Ig* was used, a QALY decrement of 2% for a scenario whereby Ig usage was reduced from [redacted] (IV)/ [redacted] (SC) to [redacted] (IV)/ [redacted] (SC) is considered to be a highly pessimistic adjustment. Although there is a lower usage of Ig in this scenario, the use of Ig as per the UK commissioning policy is expected to minimise any QALY impact of a reduction in Ig usage compared to MajesTEC-1.

Note that while QALY decrements have been applied, Janssen considers that these are highly conservative adjustments for the following reasons:

- In line with the teclistamab SPC, UK clinical feedback suggests that maintenance doses of teclistamab may be withheld as a means for managing grade 3 or 4 infections until infection improves to Grade 2 or better. Thus, in the hypothetical absence of any available Ig to manage hypogammaglobulinaemia (and therefore severe/persistent bacterial infections), there are alternative, effective forms of infection management that could be employed and that would not come at the expense of poorer clinical outcomes (e.g., reduction in treatment efficacy or a patient's quality of life).

- The MajesTEC-1 trial was conducted during the height of the COVID-19 pandemic and thus avoidable deaths were not accounted for in the current QALY.

- The DHSC has put in place demand planning strategies to mitigate any risks associated with national IVIg shortages in the UK. Thus, no usage of Ig in UK clinical practice (i.e., scenario 10a) would be highly unlikely to be realised in practice.

2) *Increase in total AE related disutility in the teclistamab arm*

   a. **Scenario 10b (IV: [redacted]; SC: [redacted] only**: the total AE related disutility in the teclistamab arm was increased by a factor of [redacted]. This was based on a total of [redacted] doses of Ig used in MajesTEC-1 compared to [redacted] doses* when Ig use was restricted to UK clinical practice. Use of Ig in MajesTEC-1 was therefore higher than use of Ig when restricted to UK clinical practice by a factor of [redacted] Accordingly, the total AE related disutility in the teclistamab arm was proportionally increased by the same factor (i.e., [redacted]), increasing the disutility from [redacted] to [redacted]. Increasing AE related utility by a factor of [redacted] results in a [redacted] change in the INHB from the base case analysis.

Janssen considers this scenario to be a conservative approach to quantifying the potential impact of reduced Ig use (per UK clinical practice) on outcomes as the total AE related disutility captures disutility related to all adverse events (with >5% frequency), including those unrelated to infections for which reduced usage of Ig would not be anticipated to impact (e.g. viral infections).

As noted above, presented ICERs in this response incorporate the revised % of teclistamab missing doses (see Appendix A for further details).

* *Formula: % x n patients in trial x number of doses (includes both IV and SC)*
[redacted]

Table 7 Scenario 10a (Ig costs excluded) and scenario 10b (UK Ig usage rates used) in which additional effects of varying IG use on outcomes have been explored (deterministic, TEC PAS price, 1.2x severity modifier applied)

Scenario	Approach	Inc costs	Inc QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Base case	Ig use as per MajesTEC-1 (IV: [redacted] SC: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Scenario 10a: No Ig included	QALY decrement of 5% in the teclistamab arm	[redacted]	[redacted]	[redacted]	[redacted]	-£4,184	-0.13	0.01
Scenario 10b: UK Ig usage rates in MajesTEC-1 (IV: [redacted]; SC: [redacted]	QALY decrement of 2% in the teclistamab arm	[redacted]	[redacted]	[redacted]	[redacted]	-£2,052	-0.05	0.02
	Total AE related disutility in the teclistamab arm increased by a factor of [redacted] i.e., [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£2,052	-0.03	0.04

Section C: Textual clarification and additional points

C1. Please provide CS, reference 24, reference 83, reference 145 and reference 176:

> 24. Janssen Data on File. UK real-world retrospective cohort study using NCRAS data (UK RW TCE study): Cohort study to establish real-world evidence for relapsed or refractory multiple myeloma pre-exposed to a proteasome inhibitor, an immunomodulatory agent and a CD38-targeted monoclonal antibody in clinical practice in England.
>
> 83. Janssen Data on File. UK Advisory Board December 2023 Meeting Minutes
>
> 145. Health Data Insight CIC. Cohort study to establish real-world evidence for multiple myeloma patients pre-exposed to a proteasome inhibitor, an immunomodulatory agent and a CD38-targeted monoclonal antibody therapy in clinical practice in England – Final study report. 2021.
>
> 176. Janssen Data on File. Advisory Board Report. December 2023.

The requested references have been provided alongside the clarification question responses. Please note that as references 83 and 176 are duplicates, only one file has been provided for both references. The reference 145 has been replaced by the Elsada et al (2021) manuscript.

References

1. Elsada A Z-MA, Knott C, Caravotas L A registry study of relapsed or refractory multiple myeloma pre-exposed to three or more prior therapies including a proteasome inhibitor, an immunomodulatory agent and CD38-targeted monoclonal antibody therapy in England. eJHaem 2021:1-5.
2. Janssen Data on File. UK Advisory Board December 2023 Meeting Minutes
3. National Institute for Health and Care Excellence. Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma. Available at: https://www.nice.org.uk/guidance/ta889/history. (Accessed 02/01/24).
4. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.
5. Janssen Data on File. MajesTEC-1 Clinical Protocol. A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma. . 2021.
6. Health Data Insight CIC. Cohort study to establish real-world evidence for multiple myeloma patients pre-exposed to a proteasome inhibitor, an immunomodulatory agent and a CD38-targeted monoclonal antibody therapy in clinical practice in England - Final study report. 2021.
7. Janssen Data on File. MajesTEC-1 Clinical Study Report (August 2023 DCO). 2023.
8. Jesus FSM, Katja CW, Kevin WS, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica 2015;100:1334-1339.

Appendix A: Correction to teclistamab relative dose intensity

In addition to the Clarification Question responses provided, Janssen have identified a minor error in the cost-effectiveness model, which means that the relative dose intensity of teclistamab was previously overestimated in the economic model; it has been necessary for us to recalculate the correct model input based upon the primary data. The relevant model cell reference is cell M27 in the 'Cost Inputs_Interventions' tab. The corrected relative dose intensity for teclistamab impacts the base case ICER and all scenarios provided in the CS.

Section B.3.5.1 of the CS notes that, of the [redacted] expected maintenance dose administrations (i.e. after the step-up period) in the MajesTEC-1 trial, [redacted] doses were administered, whereas [redacted] were skipped and not made up, resulting in [redacted] of teclistamab doses being skipped.

However, when incorporating the observed clinical data into the cost effectiveness model, the value of [redacted] expected maintenance doses in MajesTEC-1 underestimates the number of expected maintenance doses in the modelled cohort. There are three key differences between how expected doses were recorded in the trial and how dosing and time on treatment are modelled in the cost effectiveness model.

1) **Impact of cycle delays and dose delays within a cycle:**

[redacted] of patients in the trial had cycle delays and 26 patients [redacted]% had dose delays within a cycle. Those delays were not recorded as skipped doses in the trial.

2) **Number of expected doses based on the date of treatment discontinuation (for patients who discontinued treatment) or last trial observation (for patients with ongoing treatment at the time of the data cut).**

For some patients, the decision to discontinue treatment happened only after a prolonged time after the last drug exposure, during which no missed doses were recorded as part of the [redacted]% value.

Based on time to treatment discontinuation (for patients who discontinued treatment during the trial) or last trial observation date (for patients with ongoing treatment by the data cut), the expected number of maintenance doses in MajesTEC-1 is [redacted] This equates to a proportion of [redacted] of teclistamab doses missed (A1).

3) **Difference in permitted teclistamab dose frequency in MajesTEC-1 compared to the license wording**

As per the license wording, the cost effectiveness model assumes initial weekly dosing of teclistamab and allows for a switch to bi-weekly dosing. In MajesTEC-1, however, patients were permitted to switch to monthly and bi-monthly dosing. It is observed that [redacted] out of the 65 patients who switched to bi-weekly dosing subsequently switched to monthly dosing, and [redacted] of them then moved to bi-monthly dosing. If the patient changed schedule to a less frequent dosing, the total planned dose was based on the new dosing schedule.

Whilst these less frequent dosing regimens were permitted in the MajesTEC-1 trial, the economic analysis considers an NHS perspective, and therefore must consider only the licensed doses of teclistamab. As such, only weekly and bi-weekly dosing functionality is included in the model.

When combining the duration of teclistamab treatment (based on TTD, as per above) and only considering a weekly and bi-weekly treatment schedule, the total number of expected maintenance doses in MajesTEC-1 would increase to from [redacted] to [redacted]. Considering the [redacted] observed doses administered, this equates to proportion of missed doses of [redacted]%.

This percentage is calculated by comparing the recorded administered number of doses to the expected number of doses, assuming that patients receive doses weekly until they switch to a bi-weekly dosing regimen, after which point, it is assumed that patients remain on a bi-weekly dosing regimen, regardless of any further schedule changes.

The combined effect of these three differences can be expected to lead to an overestimation of the number of teclistamab doses administered in the CEM relative to the MajesTEC-1, even when the proportion of recorded skipped doses ([redacted]%) is applied.

Revised model approach for missing doses

In order to account for these issues, we calculated the proportion of teclistamab doses missed in MajesTEC-1 by comparing the number of administered doses recorded for each patient to the number of doses they would have been expected to receive had they followed the dosing schedule applied in the cost effectiveness model without deviations. The calculation of expected doses was based on the following assumptions:

- Step-up dosing would consist of 2 doses and last 7 days (in line with the assumed duration in the cost effectiveness model).
- Treatment was expected to continue as scheduled until the date of treatment discontinuation or—if treatment was ongoing at the time of data cut—until the last observation date.
- As per the license wording, patients would initially receive teclistamab weekly and could switch to bi-weekly dosing. In the base-case analysis, no further schedule changes were allowed, which means that even if the patient was switched to a less frequent dosing schedule, their expected number of doses would be calculated assuming that they should have been receiving teclistamab once every two weeks. In a scenario analysis, subsequent changes to monthly (once every 4 weeks) and bi-monthly (once every 8 weeks) schedules were also allowed. Switching back to more frequent dosing was never allowed.

These revised estimates for the proportion of missed doses are summarised in Table A1 below. The base case economic analysis has therefore been updated to use a revised proportion of [redacted] missing doses (teclistamab dose intensity of [redacted]%), based on the observed data in the MajesTEC-1 trial, with the additional adjustment applied to factor in patients switching to QM or Q2M dosing in MajesTEC-1, when this would not be allowed in the UK. The updated Company base case economic analysis is presented in Appendix B, below.

A scenario analysis, using a proportion of [redacted]% missing doses (relative dose intensity of [redacted]%) (based on the expected number of maintenance doses in the MajesTEC-1 trial, before adjusting for the use of QM and Q2M dosing regimens, is presented for completeness.

Table A1: Corrected teclistamab relative dose intensity in MajesTEC-1

	Approach to expected doses	Doses after step-up period		
		Doses administered in MajesTEC-1	Expected doses	Proportion of missed doses
Previous company base case	• If the patient in MajesTEC-1 changed schedule to a less frequent dosing, the total planned dose was based on the new dosing schedule.	[redacted]	[redacted]	[redacted]
Company corrected base case approach: expected doses as per licensed wording	• Expected doses are based on time to treatment discontinuation (for patients who discontinued treatment during the trial) or last trial observation date (for patients with ongoing treatment by the data cut). • An adjustment was made to account for patients who switched to unlicensed monthly or bi-monthly dosing regimens, to reflect the fact that these regimens would not be available in UK clinical practice and therefore a greater number of maintenance doses would be expected.	[redacted]	[redacted]	[redacted]
Scenario: switching to bi-weekly, monthly and bi-monthly schedules do not incur missed doses.	• Expected doses are based on time to treatment discontinuation (for patients who discontinued treatment during the trial) or last trial observation date (for patients with ongoing treatment by the data cut)	[redacted]	[redacted]	[redacted]

Further details regarding the calculation can be found below:

In the base case-analysis, the expected total number of doses (N_{total}) after step-up period and numbers of doses in weekly dosing period (N_{QS}) and bi-weekly dosing period (N_{Q2S}) were calculated as follows:

- If the subject did not switch to bi-weekly dosing:

$$N_{QS} = \lceil (t_{end} - 7)/7 \rceil$$

$$N_{Q2S} = 0$$

- If the subject switched to weekly dosing:

$$N_{QS} = \lceil [(t_{switch} - 1) - 7]/7 \rceil$$

$$N_{Q2S} = \left\lceil \left[t_{end} - \left(7 + 7 \times N_{QS}\right) \right]/14 \right\rceil$$

$$N_{total} = N_{QS} + N_{Q2S}$$

where t_{switch} is the time in days at which the subject switched to bi-weekly schedule and t_{end} is the time in days at which treatment was discontinued (or last trial observation was recorded if the subject remained on treatment at the data cut). An analogous calculation accounting for switches to monthly and bi-monthly dosing schedules was used in the scenario analysis.

Appendix B: Corrected base case results

Results when correcting the teclistamab missed dose percentage of [redacted]%. This is calculated by comparing the recorded administered doses to the expected number of doses based on time to treatment discontinuation (for patients who discontinued treatment during the trial) or last trial observation date (for patients with ongoing treatment by the data cut), and assuming that patients would receive doses weekly until they switch to bi-weekly schedule, and bi-weekly afterwards regardless of any further schedule changes.

Table B1: Impact of corrected % missed teclistamab doses on cost effectiveness results (base case) (deterministic, TEC PAS price, 1.2x severity modifier applied)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Company submission original base case	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Company revised base case	[redacted]	[redacted]	[redacted]	[redacted]	-£7,410	0.00	0.25

Janssen understand that a fully revised version of the economic model results contained within Document B may be needed, which include the correction. Janssen are willing to provide this updated Document B at the request of NICE or the EAG.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is the UK's biggest blood cancer research charity. We fund research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has ~120 employees and is funded primarily through donations and legacies.
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.**	Yes, we have received funding from Janssen and Bristol Myers Squibb Pharmaceuticals Janssen: • £91,290 for the Blood Cancer Action Plan • £240 for a Haematology Study Day • £180 for a CAR-T Patient Advocacy Group stakeholder meeting Bristol Myers Squibb Pharmaceuticals • £466,192 for Increasing awareness and access to clinical trials for ethnic minority communities. • £35,000 for the Blood Cancer Action Plan
4c. Do you have any direct or indirect links	None

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information for this appraisal was gathered from insights derived through our communications with the clinical, research and patient community, particularly those personally affected by multiple myeloma. We also spoke to a few patients with experience of receiving Teclistamab and to those who have experience caring for the patient group of interest. We also conducted ten in-depth interviews and two group workshops involving 11 people affected by myeloma more broadly.

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 an incurable, relapsing-remitting disease, and is therefore accompanied by very complex and diverse lived experiences however, this group of patients also share many commonalities. One patient described living with myeloma as being on both an acutely and chronically diseased state. Common symptoms include bone pain and back pain as well as fatigue or generalised weakness among others. Symptoms can affect normal functioning to varying degrees. As patients progress through subsequent treatments in the relapsed/refractory setting, many experience intensified side effects and higher physical and psychological burden. Myeloma has a marked impact on people's mental and physical health and their quality of life. Fear of the unknown has been highlighted very often by patients and carers and described as a constant 'dark cloud' over them creating a fragile lifestyle. Even during periods of remission, the knowledge that the myeloma will recur is a constant worry. One patient with myeloma expressed 'there's no certainty. That makes it difficult to plan ahead." This inability to plan for the future has a tremendous impact on both patients and families leading to increased psychological distress. Ongoing symptoms and its various manifestations also affect ability to work and function well at home. We have spoken to patients with kidney failure, who will require dialysis for the rest of their lives. Others experience weakened bones which lead to mobility issues and potentially permanent disability. The combined effects of treatment and disease mean that most people will experience a level of fatigue, even when in remission. One person shared his struggle to concentrate for long periods and make meaningful decisions. This made contributing effectively to his work/home life much more difficult. 'I did lose some of my natural enthusiasm due to the uncertainty of not knowing how the disease was responding to the various treatments and what any follow up options were.' Another person described how compression fractures in their back and neck affect their mobility and ability to stand or walk for long periods, which interferes in their daily lives. Compromised immune systems mean an elevated risk of infection and sepsis. This necessitates lifestyle changes. Other impacts of myeloma can affect people's ability to work leading to financial worries which have been expressed as 'emotionally demanding to manage.' A compromised immune system also affects people's ability to partake in activities previously enjoyed, including exercising, socialising, and travelling. Carers may need to provide personal care during periods of illness or for ongoing disabilities. This leads to increased physical and mental strain on carers and on family relationships. Carers bear the responsibility of looking out for signs of infection and ensuring that their loved one get immediate treatment if they suspect an infection. A carer whose partner was diagnosed with myeloma in 2020, describes the overnight change in their relationship: "I thought, this is it. I've driven here as your girlfriend, and I've left as a doctor, pharmacist, a nurse, a carer, like everything all rolled into one." This was not the only description of its kind. Another expressed that 'as people who do not like to call a doctor for minor ailments this has been and is, a stressful time.'

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People living with myeloma understand that even if they achieve remission, myeloma is not curable and will return at an unknown point in the future. Therefore, for some, the knowledge that there are new treatments in the pipeline are a source of reassurance and hope for them and their families. This is particularly true for people diagnosed in their thirties, forties and fifties, who have a long time to live with the condition and will potentially need multiple lines of treatment. Patients have explained that, although prior treatments have provided reasonable responses, they have not been durable and have been described as 'partially successful.' People shared their hopes that the disease would be controlled for much longer than it was. Stem cell transplants have been described as being particularly hard. Patients explained that for some, combination treatments (such as Pomalidomide and Dexamethasone) were not successful in controlling disease but have made them feel 'very delicate.' Patients have described going through the 'ordeals of several rounds of treatments with only some short-term success.' When reflecting on treatments received pre-Teclistamab, one patient expressed 'I believed I was exhausting my NHS treatment options too quickly and that made me feel helpless.' This was a sentiment strongly shared by many others we spoke to.

8. Is there an unmet need for patients with this condition?	Yes. There are huge unmet needs for this heavily pre-treated and difficult to treat patient population. Currently, people with triple-class refractory myeloma face poor outcomes. Their hopes are placed on the potential access to newer therapies such as Teclistamab and CAR-Ts. People with myeloma have expressed that amongst the most important aspects of treatment for them are maximal disease control for significant periods of time, with minimal symptoms and side effects. Significant value is placed on treatments that can lead to a good quality of life over a period that allows people to live somewhat 'normal' lives. As this group of patients would have been exposed to all the main drug classes currently available, the likelihood of their disease responding positively to the remaining alternative options is very small. Often at this point, drugs from classes patients have already been exposed to are used in different ways in the hopes of buying people more time. This leaves an increasing group of people bearing heavy physical and mental burdens, significantly reduced health related quality of life, heightened anxieties, and poorer outcomes. One person we spoke to explained 'I believe I came to the end of my NHS options in 2022/23.' One individual we spoke to expressed 'all my previous myeloma treatments, to a greater or lesser extent, made me feel quite unwell at times. I required more help from family/friends and professionals during these low points. Disease control for my previous therapies was not complete or long lasting. This led to me experiencing more symptoms/side effects including anxiety compared to this antibody treatment. Teclistamab has been a complete life changer for me, let alone a life saver.' A consultant haematologist highlighted 'we have no other options in this space that give a response rate of 60% and durable responses for a significant proportion of patients. It is much more effective than any other options.'

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	For this group of patients who currently face very limited effective treatment options on the NHS, Teclistamab offers a potentially transformative and effective option through its novel mechanism of action. This treatment can provide great relief from symptoms such as pain and fatigue. As a result, it has the potential to greatly improve people's health-related quality of life. This potential to markedly improve physical functioning and overall health is welcomed by many who would benefit from it. One person who received Teclistamab expressed he had no serious health upsets and hence zero hospital admissions since starting this medication regime. Teclistamab meets a lot of the factors described as being important to patients (please see answer to previous question). An additional advantage stems from the readily available nature of Teclistamab. Once a patient has been deemed suitable for it, the treatment can be started almost immediately, unlike therapies such as CAR-Ts. Access to this treatment in a timely fashion also mean there is no delay-associated risk of disease progression. Furthermore, its ability to provide durable responses are highly favoured by patients. One patient said that after starting Teclistamab in early 2023, his life and outlook has greatly improved. 'I do not need the support that was required pre-Teclistamab, and I am looking forward to the future with a lot more optimism and excitement.' He went onto explain that 'Teclistamab has been a brilliant drug for me, no continual side effects and complete disease control.' The subcutaneous method of administration is welcomed by patients with the treatment being described as one that 'couldn't be easier.' Additionally, once our ability to manage any potential toxicities expand, the safety data suggests the potential for Teclistamab to be administered in local centres, especially after the initial step-up dosing.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Although Teclistamab offers an effective treatment option for those who are triple-class refractory, some of the potential side effects including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and increased risk of infections, can be a cause for concern for patients and their loved ones. This would require close monitoring and supportive care. This requirement necessitates initial inpatient admission to manage the immediate toxicities which could result in higher burden for some people. Whilst we wait for the infrastructure to be further developed and for more sites to be equipped with the resources to manage treatment with bispecific antibodies, this could cause greater inconvenience for patients who live further away. When asked about the disadvantages of Teclistamab, a patient explained 'the one very minor negative aspect is that treatment is limited to a small number of hospitals which means that I have to make a two-hour journey, each way, to receive the treatment' which he concluded was a 'small price to pay for such a brilliant drug.' The burden of this, however, can vary between people and their support networks.

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.	As with many other treatments, Teclistamab may not be effective for everyone who is eligible. In the future, if it is possible to profile patients and their immune systems to determine, ahead of time, whether they will respond effectively to Teclistamab, that will be cost-effective and spare toxicities for patients who may not benefit. Also see response below.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	At the outset, Teclistamab may need to be delivered at more well-equipped centres with specifically trained healthcare professionals. This could result in short-lived inequities in access as it could pose challenges for patients who live further from centres and cannot afford, for financial or logistical reasons, to travel longer distances. However, this issue should turn less significant as it becomes more widely accessible as the infrastructure is developed. On the other hand, there is a possibility that this potential inequity in access, although expected to be temporary, could be prolonged if the right commitments to increase training and support for smaller centres are not in place for the initial stages of the step-up dosing. Issues around capacity for day units and inpatient access may also cause unequal access to this treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	One patient wished for us to highlight the potential to consider making Teclistamab available earlier in the treatment pathway. 'I feel that if this treatment was available to me earlier in my treatment regime, I may have required fewer hospital/doctor interventions, as well as being able to continue a more normal life earlier due to the fewer symptoms and or side effects I have experienced. In addition, I could have maybe avoided some of the more cytotoxic drugs which could also have reduced my risk to any future secondary cancers.' This demonstrates just how valuable this treatment can be for patients.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Myeloma is a relapsing-remitting disease. In the relapsed/refractory setting, the constant threat of recurrence means people live in a constant state of heightened anxiety and often fluctuate between 'illness' and 'wellness.' This means patients are simultaneously burdened with both the acute and chronic dimensions of this complex disease. • There are huge unmet needs faced by this heavily pretreated, triple-class refractory patients. They rely heavily on access to new treatments like Teclistamab which offer a novel mechanism of action. • Teclistamab, as a treatment option, meets a lot of the factors described as being of importance to patients when considering new treatments. • A treatment's ability to improve a patient's quality and length of life is hugely important to them and their loved ones. • Teclistamab provides patients with a clinically effective treatment option with many spill-over benefits which cannot be underestimated.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO. For more information about how we process your personal data please see our privacy notice.

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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 dealing exclusively with myeloma and related conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. 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 (Janssen) in the last 12 months. 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	-	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 January-February 2024 with relapsed/refractory myeloma patients. These interviews provide valuable experience and insight data from patients who have either had teclistimab or who are multiply relapsed and view this technology as a potential next step in their treatment pathway. - 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 and insights gathered for earlier appraisals.

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. 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. ***"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. I used to go travelling, I loved going to Egypt but I don't think that is something I will be able to do again"*** ***"When I was diagnosed, I had four vertebral fractures. It was excruciatingly painful. Even now with the damage to my bones and spine I can't really do any weight bearing activities."*** ***"I was diagnosed just before COVID. That was hard for me. I had to avoid public transport and avoid crowds. The risk of COVID was exaggerated for myeloma patients. I had to be careful when I was out. Even when going out to a restaurant. I still wear a mask. I used to go to concerts, but it is not something I think I can do safely now."*** ***"With myeloma you need to plan. Need to be aware of everything you do. You need to think about what you are doing when and if you are going to be tired or if it will make you tired. For example - if I do the hoovering I might not be fit tomorrow."*** 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] ***"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."*** 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. ***"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"*** ***"I would say I am a psychologically strong person, so I don't let it take over my thought process, but I have my dark days. For example, when you hear a lot about cancer on the news it can come to the forefront of my mind."***

[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)

	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. **"I didn't have many other options. If the trial hadn't come through, I would have been referred back to my local hospital for full chemo which in my mind is really palliative care. I wasn't calm about it, but I had accepted it. Once you are past 4/5 lines there are less and less options – only option is trials."** The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. ***"When I was diagnosed, I was 49, I had my whole life in front of me and all of that stopped. My stem cell transplant that failed. At this point due to the treatment available at the time I was told I only had 3 months to live. My relationship with my partner fell apart, I had to stop working, I sold my dentistry practice and had to move in with Mum and sister. Luckily, I was offered lenalidomide and it worked for a while. I only every seem to get 2 years at a time. It takes a while to get over something like that."*** 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. 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] ***All the treatments I have had came with side effects. It goes with the territory. The longer you have myeloma and the more treatment you have the more likely it is to come back and bite you. Everyone gets complications.*** 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. Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. 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.

	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] ***"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."*** ***"Sometimes it's tiring. Sometimes I feel sad. Sometimes I think about all the hours I have spent at the hospital and how I might have used that time otherwise. But it's all the price of love."***

[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 T-cell engagers could reverse this trend delivering good responses and long remission times at later lines. 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. **"The current treatments are OK if everything goes to plan. I don't understand why treatments can only be given in certain combos at this line. Why can't you try different things when you need them."** **"I wonder how successful are the [currently available treatments] for people like me. People with high-risk myeloma. A think a more targeted treatment makes sense.** 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. ***"I am currently relapsing for the 4th time. I never really felt like I had an incurable cancer before but it does now."*** 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] Whilst the percentage of patients achieving complete responses at earlier lines has increased in recent years with the approval of daratumumab combinations and lenalidomide maintenance there is still a significant number of patients who do not achieve full remission/complete response with standard treatments. Deep responses are associated with longer remission times and life expectancies. and treatments which deliver deep responses for patients who don't reach complete response with standard treatments are urgently needed. 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. 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. ***"I was worried about being pushed down the treatment ladder (I hate the word journey). If I had teclistamab and joined the trial, I wouldn't have the option of going back. It was quite confusing. If I went on the trial, why couldn't I go back. Suddenly I was***

	bypassing a treatment that could be good. Shutting the door on a treatment. But equally if I didn't go on the trial, I would miss an opportunity to have teclistamab." 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. ***"I would be keen to see something more out there for people like me who are young - I can't say healthy, but I feel healthy technically - and who are active. It wouldn't be nice not to give me some more treatment, given what I can contribute generally to society and my family. That's how I feel."*** Given the heterogeneous and evolving nature of myeloma, there is a need for a wide range of options at each stage of the treatment pathway. However, treatment options are extremely limited and, in some cases, non-existent at the more advanced stages of this pathway. ***"Teclistamab was my only option. I was offered palliative care a few times. My consultant previously worked at the trial centre at UCLH, and he called up to ask about trials. I never really thought I would get on one."*** 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.

[4] Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.

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 MajesTEC-1 trial showed that teclistamab delivers these benefits. In the trial, the overall response rate was 63%. 39% of patients achieved a complete response or better, and 59% achieved a very good partial response (VGPR) or better. The median progression-free survival was 11.3 months, and the median overall survival was 18.8 months.[6] Teclistamab 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 and the first B cell maturation antigen (BCMA) targeted treatment for myeloma. This addresses the need for new drugs with new mechanisms of action to combat treatment resistance. The patients we interviewed liked that teclistamab was a new class of drug with a unique way of killing myeloma cells. They were also happy to see that this treatment was for multiply relapsed, refractory patients, giving them hope that something would be available when their current treatment stopped working. ***"This sounds like something I haven't had before. It makes me optimistic about my chances of survival. Of another good summer."*** ***"This treatment really feels like a game-changer with the amount of people getting complete responses. It was for me."*** An overall response rates of 63% is a significant improvement to the treatments often used at fourth line and beyond where response rates can be as low as 30%. Many of the patients we spoke to about their experience of teclistamab were experiencing long, complete remissions for the first time after multiple lines of treatment. ***"Teclistamab gave me my first complete remission. My light chains are undetectable. When I found out I felt relieved. I know my paraproteins were going up and I knew had nowhere to go there were no other treatment options. It was a nice feeling. It is the first time that I have felt like I don't have myeloma anymore"*** ***"I have high-risk myeloma and when I started teclistamab I had my bone marrow was 60% cancerous after one month on the trial the cancer was 0%. I have just my second annual biopsy and it is still 0. All the other treatments were a disaster. I was told by people to get my affairs in order."*** ***"Teclistamab is an absolute godsend. Recently I had a bone marrow biopsy, and it was nearly undetectable. It is the longest I have ever been in remission. Longer than my stem cell transplant. It has really stabilized my myeloma. It got all of it and kept it where it should be. I have a forward look rather than looking back."***

	"I am in full remission after a year. I have gone form VGPR to full remission. I was never in full remission. I am lucky I can do all the things I want to do. My blood counts are better than I ever had on my previous treatments. This treatment is totally different to my previous treatments. I feel like a normal person. I don't have to have an IV. The regimen is very light with one day a fortnight. It is not much." ***" I feel massively fortunate to be on it. From my family's point of view, they have had years of me being ill. It is lovely for me to tell then I am in remission and the treatment is easy."*** ***" I never reached complete remission before, the lowest my paraprotein got to was 10-20. I was never a candidate for stem cell transplantation. With teclistamab I got a stringent complete response. It took a year for my paraproteins to get down to zero, my bone sample after a year showed stringent complete response. I have had myeloma for 11 years and this is my first complete response."*** The patients we interviewed also liked that the treatment did not include dexamethasone. The ability to access a novel treatment without steroids that can deliver effective remissions cannot be underestimated. **"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. Weight gain and mood swings. Can't stop talking."** **"Teclistamab is the only treatment I have had without steroids. Steroids feel like they half kill you. They make your life bad. When I was on steroids I felt like wonder woman, always on the go, cleaning cupboards, washing, ironing and only getting 2-3 hours' sleep. It made my husband's life miserable. The lack of steroids is a big plus."** It was also seen as a plus that the treatment did not exacerbate or cause peripheral neuropathy. Although side effects could be more severe in the early phases of treatment, the patients we spoke to who had received teclistamab felt the on-going treatment side effects were more manageable than previous treatments. They felt normal and could get back to doing the things

[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.
6 Moreau, P., et. al. (2022). Teclistamab in relapsed or refractory multiple myeloma. New England Journal of Medicine, 387(6), pp.495-505.

	they wanted to. They often experienced a noticeable reduction in side effects when the dosing was reduced from a weekly to bi-weekly schedule. ***"For me the teclistamab has been less damaging and less harsh on my body and my life. I got a fever after the first few doses. I was admitted and it was dealt with. Other than that, I haven't really had any side effects."*** ***"Teclistamab is absolutely wonderful, brilliant, the best treatment I have had. At first there were side effects, but they got better when the dosing changed. I feel normal."***

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. ***"Quality of life is really important but when you are looking at side effects, you need to bear in mind they are not a certainty. Not everyone gets all the side effects."*** ***"None of the side effects listed scared me. I knew I would be very well monitored. I thought - Whatever treatment I have now is a bonus. Because of the position I was in. the further you go the less options you have. The only way to stay well is to take the treatment. The benefits out way the things you are concerned about."*** ***"All treatments have side effects-> have death as a potential side effects. If you looked at the mortality figures of sepsis deaths on combination I had previously you would stop dara."*** Most of the patients we interviewed felt that the side effects associated with teclistamab were like those they had experienced whilst taking 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 main side effects patients would worry about before starting treatment were the potentially severe side effects like CRS or ICANs. However, they knew that these side effects typically happened when starting treatment. They also felt there were similar risks associated with other treatments, especially high-dose therapy and stem cell transplantation. **"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."** **"I was admitted to hospital for the 2 weeks for the set-up doses. I knew I was likely to have CRS. I had one scary episode of CRS with reduced blood pressure, sweating but they knew what it was and there was a treatment pathway, a defined action plan. There was a solution in place and it can treated and managed quickly."** Patients also felt the increased risk and number of infections was a disadvantage because having an infection could also lead to missed doses.

	"The main side effect I've experienced is infections. I get so many viruses, constant colds, sometimes more than one – rhinovirus, adenovirus. 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 CRS when restarting treatment. It means I have been in hospital a lot in the last year. I never got into the pattern of bi-weekly dosing, so I have to be checked for CRS." The need for hospitalisation and specialised care during the set-up phase was seen as a slight disadvantage because this could limit the availability of the treatment. Limited availability could have a bigger impact on people who live further from the treatment centre and those who don't drive. ***"There are quite a few hospital visits especially at the start. I live a 2-3 hour drive away from my hospital so it would be much better if this was a treatment I could take at home."***

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.

[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

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 relapsed and refractory myeloma patients. • Clinical trial data and insights from our patient interviews confirm that teclistamab can deliver the most important benefits to patients: high complete response rates, good remission times, improved life expectancy and quality of life. • There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. If approved, teclistamab could be the first NHS-commissioned T-cell engager and the first B cell maturation antigen (BCMA) targeted treatment 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 teclistamab had a positive experience and would recommend it for approval on the NHS. • Patients consider bi-weekly subcutaneous injection without steroids a distinct advantage of this treatment.

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Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	Nottingham University Hospital and the 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? Yes 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).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 11,500 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.
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.)	To control and prevent progression of myeloma, and to improve overall quality of life
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.)	As per the International myeloma working group definition of myeloma response
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The current options for treating myeloma after 3 treatments are: • Daratumamab – though many patients are now ineligible as have received daratumamab at 1st and/or 2nd line and are refractory • Pomalidomide/dexamethasone • Lenalidomide/dexamethasone -/+ ixazomib - though most patients with have received lenalidomide at 1st, 2nd or 3rd line and will be refractory and thus ineligible • Isatuximab/pomalidomide/dexamethasone - again many patients are now ineligible as have received daratumamab at 2nd line and are refractory • Bortezomib/panobinostat/dexamethasone – many patients are receiving this option after 2 treatments and hence are ineligible after 3 treatments
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are clinical guidelines for 1st line treatment of myeloma from the British Society of Haematologists: https://ukmyelomasociety.org.uk/wp-content/uploads/2022/03/Guidelines-on-the-diagnosis-investigation-and-initial-treatment-of-myeloma-a-British-Society-for-HaematologyUK-Myeloma-Forum-Guideline-March-21.pdf There are no current national guidelines reviewing the treatment options for patients with myeloma after 3 lines of treatment
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.)	There are clear treatment options available. However patients' eligibility for these treatment options vary according to what treatment they have already received, their previous response and the toxicities they have developed to that class of treatment This makes it almost impossible to define a clear pathway that encompasses all patients with myeloma.
9c. What impact would the technology have on the current pathway of care?	The availability of teclistamab after 3 lines of treatment would have a very positive impact for myeloma patients. It would broaden their treatment options and potentially increase both quality of life and prognosis for patients for whom it is suitable.
10. Will the technology be used (or is it already used) in the same way as current	We have used teclistamab in clinical trial settings and when provided on a compassionate named patient programme. There will be no change in care from these scenarios if teclsitamab is approved by NICE.

care in NHS clinical practice?	Outside of the trial setting and use on compassionate basis, teclistamab is not currently available in NHS practice and hence would give an additional line of treatment and an excellent option for suitable patients
10a. How does healthcare resource use differ between the technology and current care?	In my current experience, teclistamab requires inpatient admission when the treatment is first started, due for the need for monitoring. This is different compared to the majority of other myeloma treatments. However I appreciate that some depts. are exploring the administration and monitoring in ambulatory settings. Teclistamab is immunosuppressive and hence the requirement for immunoglobulin replacement is increased.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Haematology departments in secondary care with experience in managing the potential for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Will need to consider in-patient bed utilisation and daycase facilities; pharmacy cytolab capacity; immunoglobulin replacement treatment (cost, availability, administration capacity); doctor/nurse/pharmacy training
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Very much so
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Teclistamab would not be suitable for every patient with myeloma as would need to have adequate cardiorespiratory reserves

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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	When starting teclistamab, it can be more difficult compared with current care. For example, the need for inpatient (or ambulatory) monitoring when teclistamab is first started and the dose up- titrated. However after the 1st cycle, the administration of teclistamab is equivalent to current care. The use of immunoglobulin replacement therapy needs to be factored in to the use of teclistamab (cost, availability of drug, administration capacity)
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If a patient has disease progression despite teclistamab (as per the IMWG response definition), they should stop
15. Do you consider that the use of the technology will result in any	No

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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, teclistamab will be the first bispecific T-cell engager therapy available for myeloma patients in the UK as standard of care.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. For many patients with myeloma, there is now only the option of pomalidomide/dexamethasone after 3 lines of treatment as they will be refractory to a CD38 monoclonal antibody and have received bortezomib/vorinostat/dexamethasone and lenalidomide already. Pomalidomide/dexamethasone is less efficacious that teclistamab (in terms of progression-free survival) and can be less ideal for patients with cytopenias, pre-existing peripheral neuropathy (often from other myeloma-directed therapies) or those whom would not be suitable to receive thromboprophylaxis.
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?	There is the potential for patients treated with teclistamab to develop cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, especially at the start of treatment. Therefore, patients need to be closely monitored. This often requires inpatient admission especially during the 1st cycle of treatment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Duration of progression free survival and response were both measured in MajesTEC-1, as opposed to surrogate outcome measures
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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	No

NICE technology appraisal guidance TA783?	
21. How do data on real-world experience compare with the trial data?	Comparable

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Teclistamab is a novel and efficacious treatment for patients with relapsed or refractory myeloma • Teclistamab provides deep and durable responses for patients who currently have limited treatment options available. This translates to improved prognosis and quality of life. • Teclistamab is not suitable for all patients after 3 lines of treatment, due to the potential to develop cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome • Teclistamab does require either inpatient or ambulatory monitoring at the start of treatment • Teclistamab is immunosuppressive and the need for immunoglobulin replacement therapy needs to be factored in

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	UK Myeloma Society/ Royal college of Physicians/ Royal College of pathologists
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Myeloma society is funded by philanthropic grants, conference fees and industry grants
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.**	UK Myeloma society receives educational grants from myeloma drug and diagnostic manufacturers to support the biannual educational programmes
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.)	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)
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.)	Improvement in PFS and/or OS whilst maintaining quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	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 meet an unmet need

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	A combination of Pomalidomide and dexamethasone or Bortezomib/ Panobinostat and dexamethasone is used to treat patients after 3 prior therapies
9a. Are any clinical guidelines used in the	No current guidelines. Clinical guidelines for relapsed myeloma management led by BCSH in development

treatment of the condition, and if so, which?	
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.)	Yes the pathway of care is well defined, and treatment options are defined by reimbursed treatment options
9c. What impact would the technology have on the current pathway of care?	Teclistamab will provide a new treatment modality for patients with difficult to treat myeloma. The drug provides mechanism of action and observed higher response rates in the licensing trial
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Teclistamab will be administered in escalating disease as an inpatient for the first 2-3 doses. Subsequent doses are administered as an outpatient. The current treatment options are fully outpatient based.
10a. How does healthcare resource use differ between the technology and current care?	Teclistamab use increases risk of infection in myeloma patients treated within Majestec-1 trial. Patients were treated with on demand or prophylactic intravenous immunoglobulins to reduce risk/ severity of infection. This would become standard practice in the UK when Teclistamab is approved.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care hospitals
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment required

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Data from Majestec-1 trial provides a clinically meaningful added benefit to relapsed myeloma patients over current care
11a. Do you expect the technology to increase length of life more than current care?	Myeloma Patients who are triple class refractory (CD38 Ab, PI, IMiD) have poor survival. Teclistamab in a phase 2 trial reports a median overall survival of 21.9 months. This is a significant improvement over observed survival rates in myeloma patients at this stage of the illness.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Observed data from the Majestec-1 trial show that patient do have a meaningful improvement in Global health status and reduction in pain scores.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no subgroups to consider

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	Need for inpatient facility use for the first 2-3 doses has be factored in for treatment delivery. This may be challenging in smaller hospitals who treat myeloma patients with no dedicated inpatient bed resource. Patients may need Tocilizumab if they develop Grade 2 cytokine release syndrome. Patients who develop severe infections despite antibiotic prophylaxis, would require prophylactic immunoglobulin replacement therapy

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?	Patients reaching 4th line therapy would be eligible for this treatment. If patients progress on therapy based on routinely available blood or scan parameters, treatment will be discontinued
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?	This is a new technology in myeloma, targeting BCMA using a bispecific antibody. The results reported in a single arm Phase 1-2 Majestec-1 study is very encouraging
16a. Is the technology a 'step-change' in the management of the condition?	Yes, new target (BCMA) and a new technology bispecific antibody with significant uplift in response rates

16b. Does the use of the technology address any particular unmet need of the patient population?	The currently available drugs induce a response only in a third of patients. This new technology in a randomised study show up to 63% response with meaningful improvement in overall survival. Therefore this provides a significant uplift in response rates which deals with the significant unmet need in this patient population.
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?	Cytokine release syndrome – requires inpatient monitoring and/or Tocilizumab Low blood counts and risk of severe infections – require intravenous immunoglobulin replacement therapy, growth factors and closer monitoring and treatment of infections

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, except for subsequent therapies which may differ with what is available in the UK. Some patients received prophylactic IVIg which is not approved within current IVIg guidance
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate, Duration of response, PFS and OS
18c. If surrogate outcome measures were used, do they adequately predict	PFS is a good surrogate for Overall survival

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Non Iam aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real world evidence data available from ASH 2023
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA783?	Nil
21. How do data on real-world experience compare with the trial data?	Overall response rates are comparable to trial but patients have shorter PFS. This could be due to patients in the real world studies having had prior BCMA therapy, extramedullary disease and high risk disease (R-ISS3)

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Novel drug target - BCMA • New technology – bispecific antibody • High response rates, improved PFS and Overall survival • Qol is maintained on long term follow up • Patients need inpatient admission for first 2-3 doses which may restrict use to larger hospitals. Use of intravenous immunoglobulins is an additional health resource

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ID6333 Teclistamab for relapsed/refractory myeloma in patients who have had 3 prior therapies including a an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and who have disease progression on the last line of therapy: NHS England submission

Teclistamab wastage

1. Teclistamab is given according to the patient's weight and excepting the first 2 step up doses, teclistamab is given at a dose of 1.5mg/Kg. Toxicity is managed by dose delays rather than dose reductions. The vast majority of teclistamab dosages administered to patients is at the 1.5mg/Kg dose.
2. For such 1.5mg/Kg dosing, teclistamab comes in 153mg vials in 1.7 mLs of solution (90mg/mL). The shelf -life for a prepared syringe is 20 hours.
3. The first 4 columns in the table below are based on Table 11 from section 6.6 of teclistamab's Summary of Product Characteristics in which it can be seen that very exact volumes of injection are extracted from vials according to patient weight.
4. Vial sharing is unlikely. For significant vial sharing to occur, myeloma patients having teclistamab would have to be scheduled for one day or in a defined treatment period on the chemotherapy administration unit and would have to wait long periods of time for all the patients to be reviewed, teclistamab prescribed and the drug drawn up in an oncology pharmacy unit. This would lead to congestion and unacceptable waiting, particularly for a drug which is given weekly for the first 24 weeks. Advice to NHS from its oncology pharmacists is that such an arrangement is not feasible in chemotherapy units which are currently very stretched. Another reason for non-sharing of drawn up dosages is that the volume to be drawn up is very exact (see table below) and if not given for an individual patient, it is unlikely that drawn up doses would be used for another patient who requires the same dose on the same day.
5. NHS England has examined the distribution of weights of myeloma patients given 4th line treatment from the SACT database. For this it has used a population of 1251 patients who have been treated with the combination of isatuximab plus pomalidomide and dexamethasone. It chose this group as isatuximab is prescribed on a mg/Kg basis and hence NHS England has the greatest assurance that the weights of patients recorded in the SACT database were at the time of initiation of this combination. The database for patients prescribed pomalidomide had a considerable amount of missing weight data as this regimen is given on a flat dosing basis. The data from this SACT 1251 patient audit is shown in the two far right columns of the table below.
6. As the table below shows, wastage of teclistamab varies according to the weight of patients.
7. A calculation of the amount of wastage according to the overall weight distribution of 4th line myeloma patients indicates that there will be 28.8% wastage of teclistamab if no vial sharing occurs.
8. A small amount of vial sharing might occur in practice but it is unclear whether such sharing would lead to any significant saving. Imagine that 3 patients are treated at the same time and one comes from each of the 3 most populous weight ranges: 60-69, 70-79 and 80-89 Kg. 3 vials of drug are still to be used whether there is vial sharing or not.
9. NHS England would therefore request that this 28.8% wastage figure is used in the cost effectiveness analyses or that the costs for each patient in the modelling are dependent on the number of whole vials being used (rather than on a teclistmab cost per mg basis).

Weight of patient	Total dose mg of teclistamab	Volume of teclistamab injection mL	Number of vials of drug	Wastage % of teclistamab	Distribution of 4th line myeloma patients N=1251	% distribution of 4th line myeloma patients
35-39	56	0.62	1	63%	5	0.4%
40-44	63	0.70	1	59%	13	1.0%
45-49	70	0.78	1	54%	29	2.3%
50-59	82	0.91	1	46%	138	11.0%
60-69	99	1.1	1	35%	259	20.7%
70-79	108	1.2	1	29%	269	21.5%
80-89	126	1.4	1	18%	239	19.1%
90-99	144	1.6	1	6%	160	12.8%
100-109	153	1.7	1	0%	77	6.2%
110-119	171	1.9	2	88%	33	2.6%
120-129	189	2.1	2	76%	17	1.4%
130-139	198	2.2	2	71%	6	0.5%
140-149	216	2.4	2	59%	1	0.1%
150-160	234	2.6	2	47%	5	0.4%
		SACT data:				
Median weight 76.7Kg	**Mean weight 78.1Kg**			**Wastage by weight distribution 28.8%**		

Immunoglobulin usage

10. During the recent elranatamab appraisal (a myeloma drug with a very similar mode of action to teclistamab and with an identical therapeutic indication in its Summary of Product Characteristics), NICE heard clinical expert evidence that in responding patients, there would be considerable use of immunoglobulin in view of the induced hypogammaglobulinaemia and infection risk, the latter occurring despite the use of prophylactic antibiotics, antivirals and in some cases anti-fungal agents.
11. The overall response rate to teclistamab was 63% in the company's submission and the median duration of response was 24 months. This means that, for example, a third of all patients have responses lasting for 24 months or more. Although some endogenous immunoglobulin recovery occurs in some patients, expert myeloma opinion to NHS England is that most of the responding patients will require secondary prophylaxis with immunoglobulin for substantial periods of time given teclistamab's noteworthy efficacy in these patients. This opinion is borne out by early feedback to NHS England from the company's compassionate access program for teclistamab.

12. NHS England would suggest scenario analyses to be done for at least 50% of the trial population having at least 6 and 10 doses of immunoglobulin.

Prof Peter Clark

NHS England Clinical Lead for cancer drugs

May 2024

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Clinical expert statement

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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	Rakesh Popat
2. Name of organisation	University College London Hospitals NHS Foundation Trust
3. Job title or position	
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.	Nil
8. What is the main aim of treatment for relapsed or refractory multiple myeloma?	To prolong life and improve its quality

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
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)	In the multiply relapsed refractory setting a ≥ 30% response rate; progression free survival of ≥ 3 months is considered 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 this population. Many patients at this stage are well with a good performance status and require treatments with novel mechanisms of action or with novel targets
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?	• We follow NICE guidelines as well as EHA/ ESMO and IMWG guidelines • The pathway is well defined due to limitations in funding as determined by NICE. However there are options available and treatment is personalised according to genetic risk, refractoriness to prior treatment, performance status and patient wishes. Therefore there are some minor variabilities across England. • This technology would displace current treatment options at 4th line for many patients as it would be used in preference. However these displaced treatments (pomalidomide dex or bortezomib Panobinostat dex) can be used after this technology
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)	• Bispecific antibodies are a novel treatment and are not currently used in the NHS for myeloma (although are used in lymphoma) • They require hospitalisation or an ambulatory pathway for the initial step up dosing which is not required for standard treatments • The use of tocilizumab or equivalent is required for toxicity management • Treatment can be administer in secondary and above care centres. However the centre must be able to provide in-patient care and ICU support if required. Therefore not all secondary care hospitals can deliver this. • Additional in-patient or ambulatory capacity (e.g. hotel accommodation) will be required to administer this safely

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
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 trials of Teclistamab versus standard of care have not yet been reported; however compared to historical controls it is expected to improve both progression free and overall survival • This type of treatment is well tolerated by patients as it doesn't contain regular dexamethasone which is the commonest cause of side effects and deterioration in QOL.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• This treatment is effective for all sub-groups of myeloma however like other treatments it is less effective in high cytogenetic risk and extramedullary disease. However it is likely to still be more effective than standard treatments for these groups. • There is no apparent differential effect in different ages, sex or race
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)	• The treatment is administered by a weekly/ 2 weekly subcutaneous injection which is convenient and easy • However the requirement for hospitalisation/ ambulatory care for initial step up dosing makes it more logistically difficult • Due to the infection risk, immunoglobulin (IV or SC) is required which is an added resource and treatment burden • Screening for atypical infections is required if the patient is admitted with an infection
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	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?	Teclistamab is a bispecific antibody and represents a major advance in myeloma treatment. These demonstrate remarkable activity in patients that have stopped responding to standard treatments and are a "step-change" in treatments. The treatment has demonstrated high activity in those that have been exposed to the main 3 classes of treatment (proteasome inhibitor, immunomodulatory agent and CD38 antibody). The prognosis of such patients is otherwise poor.
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?	Side effects of cytokine release syndrome is mild and easily managed without impairing QOL. Infections are common but are mitigated with Immunoglobulins (IVIG) and prophyaxis, QOL is maintained. Initial hospitalisation is associated with a reduction in QOL but this will be improved with ambulatory pathways
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? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• The MajesTec 1 trial does represent UK patients (I recruited patients into it) and can be extrapolated to the UK population • Overall response rate, progression free and overall survival are key outcomes and were primary and secondary endpoints in the trial • PFS in the multiple relapsed population correlates with OS • No

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 658 [TA658] and TA783?	No
23. How do data on real-world experience compare with the trial data?	The response rate correlates well. The PFS appears to be shorter however real world data has short follow-up and included substantial populations that would have been excluded from trials. Toxicity profile appears the same
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. 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	No equality issues

• 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.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Teclistamab represents a “step-up” change for the treatment of relapsed myeloma patients

The treatment improves outcomes, is deliverable and improves quality of life

Careful pathway planning is required for step-up dosing

Infection management requires immunoglobulin support

Referral pathways and capacity planning for larger centres is required.

Thank you for your time.

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Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

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 Karthik Ramasamy
2. Name of organisation	UK Myeloma Society/ Royal college of Physicians/ Royal College of pathologists
3. Job title or position	Excecutive Member/ Fellow
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.	Nil
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)	
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)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma?	
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?	
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)	

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?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
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	
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?	
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?	
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? • 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?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 658 [TA658] and TA783?	

23. How do data on real-world experience compare with the trial data?	
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. 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.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

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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Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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.

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Patient expert statement

NICE National Institute for Health and Care Excellence

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	Caroline Donoghue
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 teclistamab 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 teclistamab 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 teclistamab over current treatments on the NHS please describe these. For example, are there any risks with teclistamab? 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 teclistamab 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 teclistamab? 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?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- 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

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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.

NICE National Institute for Health and Care Excellence

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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 10 May 2024.** 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	Kathryn Oddie
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**	I was diagnosed with multiple myeloma in May 2000 at the age of 38. Despite the mental challenges of living with the disease I endeavoured to live a relatively "normal" life. At this time the therapies available were aggressive chemotherapy & high dose Dexamethasone, followed by the first of 2 stem cell transplants, which caused hair loss, extreme fatigue along with the usual steroid side effects. At this point I had to end my career and finish work as a practice nurse. A second stem cell transplant followed. 5yrs later a MUD transplant (2010), was next. This had limited success. However, following these relapses I reached the end of my NHS treatment. Options available to me were palliative care or limited trails that were becoming available, I opted for the latter.
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 treatment options for refractory patients are inadequate and personally to me were palliative care only. Unable to comment as I'm not aware of current treatments for others.
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 treatments require ongoing use of steroids which can have a negative cumulative impact on physical and mental health. I personally required cataracts surgery at the age of only 52 "after having 20-20 vision all my life" this was explained to me as a side effect of long-term steroid use.

9a. If there are advantages of teclistamab 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 teclistamab 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**	Life changing, I experience minimal side effects and my general health, mental and physical are greatly improved. Compared to some previous therapies I can lead a relatively normal life. I'm able to be a wife, mother and grandmother. Minimal side effects – extended quality of life. Yes, it provides hope where previously there was none for refractory patients.
10. If there are disadvantages of teclistamab over current treatments on the NHS please describe these. For example, are there any risks with teclistamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None.
11. Are there any groups of patients who might benefit more from teclistamab 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	All, would benefit.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and teclistamab? Please explain if you think any groups of people with this condition are particularly disadvantage	Unable to comment

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?	No

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This treatment provides hope for those with refractory Myeloma.
- Reducing drugs particularly steroids to improve patient outcomes and quality of life.
- Reduced systemic side effects – giving an improved quality of life.
- Improved mental & physical health enabling a more productive normal life.
- Allowing for better outcomes for patients which would ordinarily be less favourable.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165522

Completed 16th April 2024

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sam Bryning	Critical appraisal of the economic model
Joanne McEntee	Critical appraisal of the company submission
Gillian Brearton	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

ACM	Appraisal Committee Meeting
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike Information Criterion
ASCT	autologous stem cell transplantation
ATC	average treatment effect for the control
ATE	average treatment effect
ATO	average effect on the overlap population
ATT	average treatment effect for the treated population
BCMA	B-cell maturation antigen
BIC	Bayesian Information Criterion
CASP	Critical Appraisal Skills Programme
CD38	cluster of differentiation 38
CDF	Cancer Drugs Fund
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
Dara	daratumumab
DCO	data cut-off
Dex	dexamethasone
DoR	duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
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
GHS	global health status
HCRU	healthcare resource use
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICANS	immune effector cell-associated neurotoxicity syndrome
ICER	incremental cost-effectiveness ratio
IMiD	Immunomodulatory Agent
IMWG	International Myeloma Working Group
IPD	individual patient-level data
IPTW	inverse probability of treatment weighting
IRC	independent review committee
ISS	International Staging System

ITC	indirect treatment comparison
IVIg	Intravenous Immunoglobulin
K-M	Kaplan-Meier
mAb	monoclonal antibody
MHRA	Medicines and Healthcare Products Regulatory Agency
MM	multiple myeloma
MRD	minimal residual disease
NCRAS	National Cancer Registration and Analysis Service
NE	not estimable
NHS	National Health Service
NHSE	NHS England
NICE	National Institute of Health and Care Excellence
NRCAS	National Cancer Registration and Analysis Service
ORR	overall response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressive disease
PF	progression-free
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PomDex	pomalidomide plus dexamethasone
PR	partial response
PRO	patient-reported outcome
PS	propensity score
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
Q1W	once weekly
Q2W	once every two weeks
QALY	quality-adjusted life year
RP2D	recommended phase II dose
RRMM	relapsed or refractory multiple myeloma
RW	real-world
SC	subcutaneous
sCR	stringent complete response
SD	standard deviation
SLR	systematic literature review
SMD	standardised mean differences
SmPC	Summary of Product Characteristics
TA	technology appraisal
TCE	triple-class exposed
TEAE	treatment-emergent adverse event
TSD	Technical Support Document

TTD	time to treatment discontinuation
TTNT	time to next treatment
VAS	visual analogue scale
VGPR	very good partial response

1 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.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of EAG key issues

	Summary of issue	Report sections
Issue 1	Limited clinical effectiveness data available to support the use of teclistamab or PomDex	2.4.1, 3.1.1 and 3.5.1
Issue 2	Adjusted indirect treatment comparison methods are flawed and may produce unreliable results	2.4.4, 3.5.5 and 3.8.2
Issue 3	Company approach to generating OS and PFS estimates for patients treated with PomDex does not align with approach used to generate OS and PFS estimates for patients treated with teclistamab	6.2 and 6.3
Issue 4	Company method used to generate time to treatment discontinuation estimates is not consistent with the method used to generate OS and PFS estimates for patients treated with teclistamab	6.4
Issue 5	Switching from a teclistamab Q1W regimen to a Q2W regimen is not in line with the rules set out in the teclistamab Summary of Product Characteristics	6.5
Issue 6	Health state utility values should not vary by treatment	6.6
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Issue 8	Proportion of patients treated with teclistamab who receive subsequent treatment	6.7
Issue 9	Subsequent treatments should reflect NHS practice	6.7

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a quality adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. The EAG has revised the company model by:

- attenuating company PomDex OS and PFS curves (clinician mid-point likely values)
- using a lognormal distribution to generate teclistamab TTD estimates and attenuate this curve and the company PomDex TTD curve (clinician mid-point likely values)
- switching patients treated with teclistamab who are on a Q1W regimen to a Q2W regimen from 12 months onwards
- using the same utility values for patients treated with teclistamab and PomDex
- removing AE disutilities
- assuming that the proportion of patients treated with teclistamab who receive a subsequent treatment is the same as the proportion of MajesTEC-1 trial patients treated with teclistamab who receive a subsequent treatment
- apply the UK RW TCE RRMM study subsequent treatment distribution to patients treated with teclistamab and PomDex, with an adjustment to allow patients treated with teclistamab to receive PomDex as a subsequent treatment (MajesTEC-1 trial proportion)

The EAG also provided cost effectiveness results from six scenarios:

- attenuate teclistamab and PomDex OS and PFS curves using clinician lower likely values
- attenuate teclistamab and PomDex OS and PFS curves using clinician higher likely values
- use a lognormal distribution to generate teclistamab TTD estimates and attenuate this curve using clinician lower likely values
- use a lognormal distribution to generate teclistamab TTD estimates and attenuate this curve using clinician higher likely values
- teclistamab pessimistic scenario (based on clinician likely estimates)
- teclistamab optimistic scenario (based on clinician likely estimates)

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Limited clinical effectiveness data available to support the use of teclistamab or PomDex

Report section	Section 2.4.1, Section 3.1.1 and Section 3.5.1
Description of issue and why the EAG has identified it as important	There is no direct comparative clinical effectiveness evidence available for teclistamab (intervention) versus any active comparator. Only RW registry data are available for PomDex (main comparator)
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion on the relative clinical effectiveness of teclistamab versus PomDex

EAG=External Assessment Group; PomDex=pomalidomide plus low-dose dexamethasone; RW=real-world

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Adjusted indirect treatment comparison methods are flawed and may produce unreliable results

Report section	Section 2.4.4, Section 3.5.5 and Section 3.8.2
Description of issue and why the EAG has identified it as important	The EAG identified the following methodological flaws in the company's indirect treatment comparisons: no adjustments were made for the four priority prognostic factors identified by the company and the PH assumption was violated for the OS and TTNT comparisons. The company's indirect treatment comparisons results may be unreliable
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion on the relative clinical effectiveness of teclistamab versus PomDex

EAG=External Assessment Group; IPTW=inverse probability of treatment weighting; OS=overall survival; PH=proportional hazards; PomDex=pomalidomide plus low-dose dexamethasone; TTNT=time to next treatment

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 3 Company approach to generating OS and PFS estimates for patients treated with PomDex does not align with approach used to generate OS and PFS estimates for patients treated with teclistamab

Report section	Section 6.2 and Section 6.3
Description of issue and why the EAG has identified it as important	The company attenuated distributions chosen to generate teclistamab OS and PFS projections so that 10 and 15 year estimates aligned with the mid-point of clinical expert likely values. However, when generating OS and PFS estimates for patients treated with PomDex, the company did not attenuate the curves to align estimates with clinical expert likely values
What alternative approach has the EAG suggested?	The EAG has attenuated company model OS and PFS distributions for patients treated with PomDex so that the OS and PFS curves generate estimates that align with the mid-point of the company clinical expert likely values at 10 and 15 years
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £1,890
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion on the relative long-term clinical effectiveness of teclistamab versus PomDex

EAG=External Assessment Group; NMB=net monetary benefit; OS=overall survival; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone

Issue 4 Company method used to generate time to treatment discontinuation estimates is not consistent with the method used to generate OS and PFS estimates for patients treated with teclistamab

Report section	Section 6.4
Description of issue and why the EAG has identified it as important	For consistency, the company approach used to generate PFS and OS estimates for patients treated with teclistamab should have been used to generate TTD estimates, i.e., 1) teclistamab TTD should have been modelled using the best-fitting TTD distribution (lognormal) and the curve attenuated so that 10 and 15 year estimates aligned with clinician 10 and 15 year estimates and 2) the company curve used to generate PomDex TTD should have been attenuated so that 10 and 15 year estimates aligned with clinician 10 and 15 year estimates
What alternative approach has the EAG suggested?	The EAG has used the lognormal distribution (best fitting distribution) to generate teclistamab TTD estimates and has attenuated this curve and the company PomDex TTD curve so that TTD estimates align with the mid-point of the company clinical expert likely values at 10 and 15 years
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £3,005
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion on the relative long-term clinical effectiveness of teclistamab versus PomDex

EAG=External Assessment Group; NMB=net monetary benefit; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation

Issue 5 Switching from a teclistamab Q1W regimen to a Q2W regimen is not in line with the rules set out in the teclistamab Summary of Product Characteristics

Report section	Section 6.5
Description of issue and why the EAG has identified it as important	The approach used by the company to model switching from a teclistamab Q1W regimen to a Q2W regimen does not reflect the switching rules set out in the teclistamab SmPC
What alternative approach has the EAG suggested?	The EAG has revised the company model so that patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportions who switch at each time point are determined by MajesTEC-1 trial data
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £1,851
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on when NHS patients might switch teclistamab treatment regimens

EAG=External Assessment Group; NHS=National Health Service; NMB=net monetary benefit; Q1W=once weekly; Q2W=every 2 weeks; SmPC=Summary of Product Characteristics

Issue 6 Health state utility values should not vary by treatment

Report section	Section 6.6
Description of issue and why the EAG has identified it as important	In the company model, PF and PD health states utility values vary by treatment. Clinical advice to the company was that the same (MajesTEC-1 trial) utility values should have been used to reflect HRQoL for patients treated with teclistamab and patients treated with PomDex
What alternative approach has the EAG suggested?	The EAG has used the same PF and PD health state utility values (derived from MajesTEC-1 trial data) for patients treated with teclistamab and patients treated with PomDex
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £4,836
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; HRQoL=health-related quality of life; NMB=net monetary benefit; PD=progressed disease; PF=progression-free; PomDex=pomalidomide plus low-dose dexamethasone

Issue 7 Application of a one-off utility decrement for patients who experience TEAEs represents double counting

Report section	Section 6.6
Description of issue and why the EAG has identified it as important	The company has applied a one-off utility decrement to account for the effect of TEAEs on HRQoL; as company utility values are derived from trial data, this represents double counting
What alternative approach has the EAG suggested?	The EAG has revised the company model so that the one-off decrement for patients who experience TEAEs is not applied
What is the expected effect on the cost effectiveness estimates?	The EAG revision increases the deterministic NMB by £321
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; HRQoL=health-related quality of life; NMB=net monetary benefit; TEAE=treatment emergent adverse events

Issue 8 Proportion of patients treated with teclistamab who receive subsequent treatment

Report section	Section 6.7
Description of issue and why the EAG has identified it as important	The company has estimated the proportion of patients treated with teclistamab who receive subsequent treatment based on real world evidence; the EAG considers that the proportion should reflect the experience of the MajesTEC-1 trial teclistamab population
What alternative approach has the EAG suggested?	The EAG has revised the company model so that the proportion of patients treated with teclistamab who receive subsequent treatment matches the proportion of MajesTEC-1 trial patients who received subsequent treatment
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £450
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; NMB=net monetary benefit

Issue 9 Subsequent treatments should reflect NHS practice

Report section	Section 6.7
Description of issue and why the EAG has identified it as important	In the company model, subsequent treatments received by patients vary by treatment. Subsequent treatments should reflect treatments available to NHS patients and should be the same for patients treated with teclistamab and patients treated with PomDex, with the exception that some patients receiving teclistamab may receive PomDex as a subsequent treatment
What alternative approach has the EAG suggested?	The EAG has revised the company model so that the types (and frequencies) of subsequent treatments are the same for patients treated with teclistamab and PomDex, with an adjustment to allow patients treated with teclistamab to receive PomDex as a subsequent treatment (MajesTEC-1 trial proportion)
What is the expected effect on the cost effectiveness estimates?	The EAG revision decreases the deterministic NMB by £552
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; NHS=National Health Service; NMB=net monetary benefit; PomDex=pomalidomide plus low-dose dexamethasone

1.6 Summary of EAG's preferred assumptions and resulting ICERs per QALY gained

Table B Probabilistic results for the comparison of teclistamab versus PomDex, PAS price for teclistamab

EAG revisions†	Incremental		ICER	NMB*	NMB change
	Cost	QALYs (x1.2 multiplier)	£/QALY		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	
A1. Company clarification base case with PSA corrected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred base case (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
† The EAG PSA runs exclude variation of unit costs
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; PAS=Patient Access Scheme; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

Modelling errors identified and corrected by the EAG are described in Section 6. For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.9.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this National Institute for Health and Care Excellence (NICE) appraisal is on teclistamab (brand name: Tecvayli™) as a treatment option for patients with relapsed or refractory multiple myeloma (RRMM) who have received ≥3 prior lines of treatment, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-cluster of differentiation 38 (CD38) monoclonal antibody (mAb) and have demonstrated disease progression on the last therapy received; these patients are referred to as patients with triple-class exposed (TCE) RRMM.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company during the clarification stage.

2.2 Background

2.2.1 Multiple myeloma

Myeloma is a rare, incurable type of haematological cancer that develops from bone marrow plasma cells. Patients are diagnosed with multiple myeloma (MM) when more than one bone marrow site is affected.[1]

Myeloma accounts for approximately 2% of UK cancer cases.[2] In the UK, approximately 6,000 patients are diagnosed with myeloma each year and 45% of cases are diagnosed in patients aged ≥75 years; myeloma is rarely diagnosed in patients aged <40 years.[2] Myeloma is more commonly diagnosed in men than in women and, compared to the White ethnic group, myeloma is more commonly diagnosed in the Black ethnic group and less commonly diagnosed in the Asian ethnic group.[2] The 5-year and 10-year survival rates for patients in England with myeloma are 55% and 30%, respectively.[3]

2.2.2 TCE RRMM

In the International Myeloma Working Group (IMWG) consensus recommendations:[4]

- 'relapsed' MM is defined as "previously treated myeloma that progresses and requires the initiation of salvage therapy"
- 'refractory' MM is defined as myeloma "that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy".

TCE refers to patients who have received at least an IMiD, a PI and an anti-CD38 mAb, either as a monotherapy or as part of a combination therapy.

2.2.3 Teclistamab

Teclistamab is a humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody that binds to the B-cell maturation antigen (BCMA) expressed on malignant MM plasma cells and the CD3 receptor complex expressed on T cells.[5] Teclistamab has dual binding sites and is able to recruit CD3-positive T-cells to BCMA-positive MM plasma cells, thus promoting T cell activation and the subsequent lysis of BCMA-positive MM plasma cells.[6]

Teclistamab is administered via subcutaneous (SC) injection and is available as 10mg/ml and 90mg/ml solutions.[7] The recommended dose is 1.5mg/kg once weekly (Q1W), preceded by step-up doses of 0.06mg/kg on Day 1 and 0.3mg/kg on Day 3. Patients who achieve a complete response or better (≥CR; i.e., patients who achieved a CR or a stringent CR [no detectable plasma cells in the bone marrow or myeloma proteins in the serum or urine]) for ≥6 months may reduce the dose frequency to once every two weeks (Q2W) 1.5mg/kg SC injections.[7]

Dose reductions are not recommended and therefore dose delays may be required to manage treatment-related adverse events (TRAEs).[7] For re-initiation of teclistamab, step-up doses should be repeated as specified in the Summary of Product Characteristics (SmPC).[7]

Teclistamab has a conditional licence from the European Medicines Agency (EMA)[8] and a conditional licence from the Medicines and Healthcare products Regulatory Agency (MHRA)[9] as a monotherapy for the treatment of adult patients with RRMM, who have received ≥3 prior therapies, including an IMiD, a PI and an anti-CD38 mAb and have demonstrated disease progression on the last therapy received.

2.3 Company's overview of current service provision

The company has presented the current NHS treatment pathway for patients with MM and the positioning of teclistamab, should teclistamab be recommended by NICE (CS, Figure 2). The company pathway was informed by the NICE myeloma diagnosis and management guidelines (NG35),[10] which were most recently updated in October 2018.

A description of the first-line, second-line and third-line treatment options for NHS patients with MM is provided in Appendix 1, Section 8.1.

The following treatments are recommended by NICE as fourth-line treatment options, depending on previous line of treatment, but regardless of transplantation eligibility in the first-line setting:

- pomalidomide plus dexamethasone (PomDex) (TA427)[11]
- panobinostat plus bortezomib and dexamethasone (TA380)[12]

- ixazomib plus lenalidomide and dexamethasone (TA505)[13]
- isatuximab plus pomalidomide and dexamethasone; however, only NICE recommended for use within the Cancer Drugs Fund (TA658)[14]
- daratumumab monotherapy (TA783)[15]
- lenalidomide with dexamethasone (TA171)[16]

Clinical advice to the EAG agrees with the company (CS, p31) that patients with relapsed MM receive similar treatment options in the second-line, third-line and fourth-line settings, regardless of transplantation eligibility in the first-line setting, and that prior autologous stem cell transplantation (ASCT) does not affect response to fourth-line treatment.

Clinical advice to the company (CS, p12) was that 90% of patients with TCE RRMM receive PomDex in the fourth-line setting.[17] Clinical advice to the EAG is that:

- close to 90% of patients with TCE RRMM receive PomDex in the fourth-line setting
- a few patients who have sufficient functional bone marrow reserve and who are contraindicated for an IMiD may receive panobinostat plus bortezomib and dexamethasone (PanBorDex) in the fourth-line setting
- the remaining 10% of patients with TCE RRMM enter clinical trials or receive compassionate use cancer drugs.

The company has positioned teclistamab as an alternative treatment to PomDex for patients with TCE RRMM who have received ≥3 prior lines of treatment (CS, Figure 6 and p34). The company's positioning of teclistamab is in line with its conditional MHRA marketing authorisation,[9] i.e., as monotherapy for the treatment of adult patients with RRMM who have received ≥3 prior therapies, including an IMiD, a PI, and an anti-CD38 mAb and have demonstrated disease progression on the last therapy received.

2.4 Critique of company's definition of decision problem

A summary of the final scope[18] issued by NICE and the decision problem addressed by the company is presented in Table 1. More information regarding key issues is provided in Section 2.4.1 to Section 2.4.7.

Table 1 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed by the company with rationale	EAG comments
Population	People with relapsed or refractory multiple myeloma after ≥3 prior treatments including an IMiD, a PI and an anti-CD38 Ab and have demonstrated disease progression on the last treatment	Adult patients with relapsed and refractory multiple myeloma, who have received ≥3 prior therapies including an IMiD, a PI and an anti-CD38 Ab and have demonstrated disease progression on the last therapy	As per NICE scope
Intervention	Teclistamab	Teclistamab	As per NICE scope
Comparator(s)	• Lenalidomide plus dexamethasone • Panobinostat plus bortezomib and dexamethasone • Pomalidomide plus low-dose dexamethasone • Daratumumab monotherapy • Ixazomib plus lenalidomide and dexamethasone • Cyclophosphamide plus dexamethasone • Isatuximab plus pomalidomide and dexamethasone (subject to NICE evaluation) • Elranatamab (subject to NICE evaluation)	Pomalidomide plus low-dose dexamethasone (PomDex) The company rationale for including PomDex as the only relevant comparator was provided in CS, Table 1	Clinical advice to the EAG agrees that PomDex is the most relevant comparator for this appraisal (See Table 2). The source of PomDex data is the UK RW TCE RRMM study; the EAG and the company agree that this study has serious overall risk of bias. In the absence of PomDex clinical trial evidence, the company carried out adjusted ITCs to compare the effectiveness of teclistamab versus PomDex. However, the EAG identified methodological flaws in the ITCs (see Section 2.4.4). The EAG considers that the ITC results may be unreliable
Outcomes	• OS • PFS • Response rates • AEs of treatment • HRQoL	Outcomes included in the submission are: **Survival rates:** • OS and PFS **Response rates:** • ORR, DoR, ≥VGPR, CR, sCR, ≥CR, PR, MR, SD and PD **Other outcomes:** • AEs, TTD, TTNT, MRD negativity rate and HRQoL	As per NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The economic analysis aligns with that described in the NICE decision problem	As per NICE scope

	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account		

Ab=antibody; AEs=adverse events; CDF=Cancer Drugs Fund; CR=complete response; ≥CR=complete response or better; DOR=duration of response; EAG=External Assessment Group; HRQoL=health-related quality of life; IMiD=immunomodulatory agent; IsaPomDex=isatuximab plus pomalidomide and dexamethasone; ITC=indirect treatment comparison; MR=minimal response; MRD=minimal residual disease; NICE=National Institute for Health and Care Excellence; ORR=overall response rate; OS=overall survival; PD=progressed disease; PFS=progression-free survival; PI=proteasome inhibitor; PomDex=pomalidomide plus low-dose dexamethasone; PR=partial response; SD=-stable disease; sCR=stringent complete response; TTD=time to treatment discontinuation; TTNT=time to next treatment; ≥VGPR=very good partial response or better

2.4.1 Sources of clinical effectiveness evidence

Intervention: teclistamab

Teclistamab clinical effectiveness evidence is available from the MajesTEC-1 trial,[19] an ongoing, three-part, phase I/II, open-label, multicentre, international, single-arm trial of teclistamab monotherapy for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI, and an anti-CD38 mAb. The company also reported clinical effectiveness evidence results from two recently published, real-world (RW), retrospective studies of teclistamab for patients with TCE RRMM (the Dima study[20] and the Riedhammer study[21]).

Comparator: PomDex

PomDex is the main comparator to teclistamab. In the absence of PomDex clinical trial evidence, the company used individual patient-level data (IPD) for patients with TCE RRMM and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 1 who received PomDex from the UK RW TCE RRMM study. The UK RW TCE RRMM study is a registry study of NHS England (NHSE) cancer data, and data from linked datasets, that are available through the National Cancer Registration and Analysis Service (NCRAS).[22]

2.4.2 Population

The population addressed by the company largely matches the population specified in the final scope issued by NICE. The EAG notes that the population specified in the final scope issued by NICE was not restricted by age; clinical advice to the EAG is that it was reasonable to restrict the population to adults as MM is rarely observed in children or young adults.

Clinical trial evidence: teclistamab

Clinical advice to the EAG is that the baseline characteristics of the MajesTEC-1 trial All Treated Analysis Set patients (N=165) represent the characteristics of NHS patients with TCE RRMM who have received ≥3 prior lines of treatment, with the exceptions that, compared with NHS patients, MajesTEC-1 trial patients are, on average, younger (mean age: [redacted] years) and fitter (ECOG PS 0 to 1) and fewer patients have high risk cytogenetics ([redacted], [redacted]). Clinical advice to the company and to the EAG is that MajesTEC-1 trial patients are also likely to be more heavily pre-treated than NHS patients with TCE RRMM but that, overall, MajesTEC-1 trial results are generalisable to NHS patients.

Real-world evidence: teclistamab

Clinical advice to the EAG is that the Dima study[20] and the Riedhammer study[21] populations were less fit and had a worse prognosis than the MajesTEC-1 trial All Treated Analysis Set

population and therefore patients enrolled in these two studies may be more representative of NHS patients with TCE RRMM than MajestTEC-1 trial patients.

Real-world evidence: PomDex

Clinical advice to the EAG is that, overall, the UK RW TCE RRMM study population is more representative of NHS patients with TCE RRMM than the MajesTEC-1 trial, the Dima study[20] and the Riedhammer study[21] populations because the data are specific to the UK and the median number of prior lines of treatment is more similar to the number of treatments received by NHS patients.

However, clinical advice to the EAG is that the UK RW TCE RRMM study population is not wholly representative of NHS patients as:

- median time from diagnosis to first dose of PomDex in the UK RW TCE RRMM study was shorter than would be expected for NHS patients with TCE RRMM
- the UK RW TCE RRMM study included patients with TCE RRMM who were diagnosed with MM over 10 years ago (January 2013 to 31 December 2021) and since then NHS RRMM clinical practice has evolved.

The company considered (and the EAG agrees) that, compared with the MajesTEC-1 trial All Treated Analysis Set population, the UK RW TCE RRMM study PomDex cohort better represented the target population for this appraisal and therefore it was appropriate to match data from the MajesTEC-1 trial All Treated Analysis Set population to the UK RW TCE RRMM study PomDex cohort to inform adjusted indirect treatment comparisons (ITCs).

The EAG considers that none of the TCE RRMM study populations described in the CS are wholly representative of NHS TCE RRMM patients; nevertheless, overall, the EAG considers that the results from the MajesTEC-1 trial, the Dima study,[20] the Riedhammer study[21] and the UK RW TCE RRMM study are generalisable to NHS patients.

2.4.3 Intervention

The company has presented evidence for teclistamab as per its conditional EMA[8] and MHRA[9] licences (See Section 2.2.3).

The EMA approved a conditional marketing authorisation for teclistamab based on MajesTEC-1 trial data. In the European Public Assessment Report (EPAR),[8] it is stated that, to fulfil the conditional marketing authorisation, the company must provide:

- the MajesTEC-3 trial results by March 2028 to confirm the efficacy and safety of teclistamab as a monotherapy for the treatment of adult patients with RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb and have demonstrated disease progression on the last treatment received

- the final MajesTEC-1 trial clinical study report (CSR) by 30 September 2025 to confirm the duration of response and long-term safety of teclistamab for patients with MM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb.

2.4.4 Comparators

The company considers (and clinical advice to the EAG agrees) that PomDex is the main comparator to teclistamab for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb and whose disease progressed on the last treatment received. Clinical advice to the EAG is that it is reasonable for the company to exclude all other comparators specified in the final scope issued by NICE. A summary of the company's rationale for excluding all other comparators specified in the final scope issued by NICE and additional clinical advice to the EAG is provided in Table 2.

Table 2 Summary of the company's rationale for excluding comparators specified in the final scope issued by NICE

Comparator	Company's reason for exclusion	Clinical advice to the EAG
IsaPomDex	• NICE recommended IsaPomDex for use within the CDF and therefore IsaPomDex is not currently routinely available in the NHS • 95% of patients who receive IsaPomDex are anti-CD38 mAb-naïve and therefore do not have TCE RRMM • Patients who previously received daratumumab (an anti-CD38 mAb) and who progressed on treatment are considered to be anti-CD38 refractory and therefore are not eligible to receive IsaPomDex at fourth-line	Agrees with company rationale
Elranatamab	There is an ongoing NICE technology appraisal[23] for elranatamab and therefore it is not routinely available in the NHS	Agrees with company rationale
LenDex	LenDex is predominantly used third-line and can be used first-line. LenDex is rarely used fourth-line	Agrees with company rationale
PanBorDex	PanBorDex is no longer used due to toxicity concerns	PanBorDex may be a fourth-line treatment option for a few patients who have sufficient functional bone marrow reserve and who are contraindicated for an IMiD, however, PanBorDex is predominantly used fifth-line
Daratumumab monotherapy	• Rarely used fourth-line • Daratumumab is the only routinely available anti-CD36 mAb in the NHS and therefore patients will need to be daratumumab-refractory to be eligible to receive teclistamab	Agrees with company rationale
IxaLenDex	LenDex is predominantly used third-line and can be used first-line and therefore patients would not be re-challenged with IxaLenDex fourth-line	Agrees with company rationale
CycloDex	Clinical advice to the company was that CycloDex would be used third-line or as a salvage option at fifth-line or later	• Agrees with company rationale • CycloDex is a palliative treatment option and is mostly used to treat very frail patients (ECOG PS 3 or 4) at fifth-line or later

CDF=Cancer Drugs Fund; CS=company submission; CycloDex=cyclophosphamide plus dexamethasone; EAMS=Early Access to Medicines Scheme; ECOG PS=Eastern Cooperative Oncology Group performance status; IMiD=immunomodulatory agent; IsaPomDex=isatuximab plus pomalidomide and dexamethasone; IxaLenDex=ixazomib plus lenalidomide and dexamethasone; LenDex=lenalidomide plus dexamethasone; mAb=monoclonal antibody; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PanBorDex=panobinostat plus bortezomib and dexamethasone; TCE RRMM=triple-class exposed relapsed or refractory multiple myeloma
Source: CS, Table 1

The company carried out adjusted ITCs to compare the effectiveness (overall survival [OS] and time to next treatment [TTNT]; TTNT was used as a proxy for progression-free survival [PFS]) of teclistamab versus PomDex using IPD from the MajesTEC-1 trial and IPD from the UK RW TCE RRMM study. The EAG considers that the company ITCs are methodologically flawed and results may be unreliable.

2.4.5 Outcomes

Clinical advice to the EAG is that the outcomes listed in the final scope issued by NICE are the most relevant outcomes for patients with TCE RRMM. The MajesTEC-1 trial primary endpoint was overall response rate (ORR), as assessed by the independent review committee (IRC) based on IMWG[24] criteria. Other key outcomes include duration of response (DoR), OS, PFS, minimal residual disease (MRD) negativity rate, health-related quality of life (HRQoL) and adverse events (AEs). Definitions of MajesTEC-1 trial outcome measures are provided in the CS (CS, Table 11).

The company provided indirect evidence for the comparison of teclistamab versus PomDex for key outcomes: OS and TTNT (as a proxy for PFS). ORR, HRQoL and safety outcomes were not reported in the UK RW TCE RRMM study. Therefore, the company was unable to provide indirect evidence for the comparison of teclistamab versus PomDex for these outcomes.

2.4.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year period and costs were considered from an NHS and Personal and Social Services (PSS) perspective.

The company states that teclistamab will be available to the NHS at a confidential discounted price (Patient Access Scheme [PAS]). The cost effectiveness results presented in this report have been calculated using the confidential price of teclistamab and list prices for all other drugs.

The company QALY short fall analysis results show that treatment with teclistamab meets the criteria for a x 1.2 severity weight when compared with PomDex.

2.4.7 Subgroups

No subgroups were specified in the final scope issued by NICE, however, the company provided (CS, Section 2.7) subgroup analyses results for ORR stratified by:

- baseline disease characteristics including International Staging System (ISS) stage, revised ISS, cytogenetic risk, percentage plasma cells, tumour BCMA expression and extramedullary plasmacytomas (CS, Figure 23)
- baseline patient characteristics including age, sex, race, renal function and ECOG PS (CS, Figure 24)
- prior therapy including number of lines of prior therapy, refractory status, prior ASCT, prior allogenic stem cell transplant and type of myeloma (CS, Figure 25).

Some subgroup populations were small (e.g., for prior allogenic stem cell transplant, yes: n=[redacted]) and therefore CIs were often wide.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support of the use of teclistamab as a treatment option for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb and whose disease progressed on the last treatment received.

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify and select clinical effectiveness evidence relating to treatments for patients with TCE RRMM. Full details of the company's methods are presented in the CS (Appendix D). The company's literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the Liverpool Reviews and Implementation Group (LR*i*G) in-house systematic review checklist is summarised in Table 3. The EAG considers that the company's systematic review methods were appropriate.

Table 3 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1.2, Table 8
Were appropriate sources searched?	Yes	CS, Appendix D.1.1, pp7-9
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.1, p7
Were appropriate search terms used?	Yes	CS, Appendix D.1.1, Table 1 to Table 7
Were the eligibility criteria appropriate to the decision problem?	Mostly	CS, Appendix D.1.2, Table 8 The SLR eligibility criteria included studies of "treatments under investigation for RRMM provided as a single-agent or a combination treatment" (CS, Appendix D.1.2, Table 8) and thus the company SLR was broader (with regard to interventions and comparators) than was required to address the decision problem described in the final scope issued by NICE
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2, p38
Was data extracted by two or more reviewers independently?	Yes	CS, Appendix D.1.2, p39 One reviewer extracted data and the data were then checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partly	CS, Section B.2.5, Table 12 (Downs and Black checklist[25] for the MajesTEC-1 trial) and CS, Appendix D.2.6, Table 19 to Table 23 (ROBINS-I tool[26] for the UK RW TCE RRMM study) The company quality assessed the MajesTEC-1 trial using the Downs and Black checklist[25] for non-randomised trials. The EAG considers that the Downs and Black checklist was not the appropriate quality assessment tool to use because it considers studies with ≥2 treatment groups (see Section 3.2.3) The EAG quality assessed the MajesTEC-1 trial using the CASP checklist[27] for cohort studies. The EAG assessment reached the same conclusion as the company assessment, i.e., that the MajesTEC-1 trial is of good methodological quality
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D.1.2, p40 One reviewer quality assessed studies and quality assessments were then checked by a second (independent) reviewer
Were attempts to synthesise evidence appropriate?	Partly	ITCs were performed. See Section 3.5.3 for the company's methods and Section 3.5.5 for the EAG's critique of the indirect evidence syntheses

CASP=Critical Appraisal Skills Programme; CS=company submission; EAG=External Assessment Group; ITCs=indirect treatment comparisons; LR*i*G=Liverpool Reviews and Implementation Group; NICE=National Institute for Health and Care Excellence; ROBINS-I=Risk Of Bias In Non-randomized Studies of Interventions; RRMM=relapsed or refractory multiple myeloma; RW=real-world; SLR=systematic literature review; TCE=triple-class exposed
Source: LR*i*G in-house checklist

3.1.1 Included trials

The company SLR eligibility criteria were broader (with regard to interventions and comparators) than required to address the decision problem described in the final scope issued by NICE. In addition to studies of teclistamab, the company searched for studies of

RRMM monotherapies and combination RRMM treatments including, but not limited to, thalidomide, lenalidomide, pomalidomide, bortezomib, ixazomib, carfilzomib, daratumumab, isatuximab, elotuzumab, selinexor, belantamab mafodotin and idecabtagene vicleucel.

The company SLR identified 218 studies (CS, Appendix D.2.1, Table 9); however, only one study, the MajesTEC-1 trial, included teclistamab (see Section 3.2.1 to Section 3.2.4 for more details). The identified studies that included the relevant comparator, PomDex, did not report data for patients with TCE RRMM and therefore were not relevant (CS, Appendix D.2.1, p41).

Real-world evidence

In the absence of PomDex clinical trial evidence for patients with TCE RRMM, the company conducted a registry study of patients with TCE RRMM in England using NCRAS[22] data referred to as the UK RW TCE RRMM study (see Section 3.4.2, Section 3.4.3, Section 3.5.1 and Section 3.5.2 for more details). The UK RW TCE RRMM study publication (Elsada 2021[28]) was identified by the company's SLR but was incorrectly excluded during the title and abstract screening (Clarification Question A1).

The company also reported ORR results from two recently published RW retrospective studies of teclistamab for patients with TCE RRMM, the Dima study[20] and the Riedhammer study[21] (see Section 3.4.1 and Section 3.4.3 for more details). These two RW studies[20,21] were not identified by the company SLR because they were published after the most recent search date (October 2023).

3.2 Direct clinical effectiveness evidence

Teclistamab clinical effectiveness evidence was only available from the MajesTEC-1 trial.

3.2.1 Characteristics of the MajesTEC-1 trial

The MajesTEC-1 trial is an ongoing, three-part, phase I/II, open-label, multicentre, international single-arm trial of teclistamab monotherapy for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI, and an anti-CD38 mAb.

The MajesTEC-1 trial comprises three parts:

- phase I (part 1): a dose escalation phase that identified the teclistamab recommended phase II dose (RP2D)
- phase I (part 2): a dose expansion phase that investigated the safety and tolerability of the teclistamab RP2D
- phase II (part 3): investigates the efficacy and safety of the teclistamab RP2D and consists of three patient cohorts
    - cohort A: patients with TCE RRMM who received ≥3 prior lines of treatment including a PI, an IMiD, and an anti-CD38 mAb

- cohort B: patients with TCE RRMM who received ≥4 prior lines of treatment including a PI, an IMiD, and an anti-CD38 mAb; cohort B was not open for enrolment at the time of the final data cut
- cohort C: patients with TCE RRMM who received ≥3 prior lines of treatment including a PI, an IMiD, anti-CD38 mAb and anti-baseline B-cell maturation (BCMA) treatment (chimeric antigen receptor [CAR]-T cells or an antibody drug conjugate [ADC])

The MajesTEC-1 trial investigators determined the RP2D as 1.5mg/kg teclistamab SC Q1W until disease progression or unacceptable toxicity; this is the conditional MHRA[9] licensed dose.

The MajesTEC-1 trial population relevant to this appraisal (N=165) includes 40 patients from phase I (part 2) who received the RP2D and 125 patients from phase II Cohort A (CS, Table 5). In the CS, the company collectively refers to this population as the All Treated Analysis Set (CS, p43). Patients recruited to the MajesTEC-1 trial part 2 and part 3 were enrolled at 35 sites in nine countries (including three UK sites) between March 2020 and August 2021.[29]

The company considered (CS, p39 and p43) that evidence from phase II Cohort C patients was not relevant to this appraisal because Cohort C patients had received anti-BCMA treatment which is not routinely available in NHS clinical practice. Clinical advice to the EAG agrees that it was reasonable to exclude this population.

Key MajesTEC-1 trial eligibility criteria[30] were similar for both trial phases and included the following:

- patients aged ≥18 years
- documented diagnosis of MM according to IMWG[24] diagnostic criteria
- RRMM following prior treatment with a PI, an IMiD and an anti-CD38 mAb, in any order (patients who could not tolerate a PI or an IMiD were also eligible for inclusion)
- ECOG PS 0 or 1
- for part 3 only, RRMM after ≥3 prior lines of treatment (number of prior lines of treatment was not an eligibility criterion for part 1 and part 2)
- for part 2 and part 3, MM must have been measurable per current IMWG[24] published guidelines by central laboratory assessment.

Full eligibility criteria are presented in the trial protocol.[30]

The primary outcome is ORR, as assessed by the IRC based on IMWG[24] criteria. Other key outcomes include DoR, OS, PFS, MRD negativity rate, HRQoL and AEs. Most of the data presented in the CS are from the 22 August 2023 data cut-off (DCO). Earlier data cuts include September 2021, March 2022 and January 2023. A summary of data from earlier DCOs is provided in CS, Table 13.

3.2.2 Characteristics of MajesTEC-1 trial patients

The MajesTEC-1 trial All Treated Analysis Set population baseline characteristics and prior therapy details are provided in the CS (Table 7 and Table 8, respectively).

Clinical advice to the EAG is that the baseline characteristics of the MajesTEC-1 trial All Treated Analysis Set patients are representative of NHS patients with TCE RRMM who have received ≥3 prior lines of treatment with the exceptions that MajesTEC-1 trial patients are, on average, younger (mean age: [redacted] years), fitter (ECOG PS 0 to 1) and fewer patients have high risk cytogenetics ([redacted], [redacted]) than NHS patients with TCE RRMM.

Clinical advice to the EAG and the company is that:

- MajesTEC-1 trial patients are likely to be more heavily pre-treated than NHS patients with TCE RRMM ([redacted]/165 patients [redacted] had received ≥4 prior lines of treatment) and therefore MajesTEC-1 trial results may underestimate the efficacy of teclistamab
- compared with NHS patients, a higher proportion of MajesTEC-1 trial patients had previously received ASCT (approximately 50% versus 135/165, 81.8%); prior ASCT is not an important prognostic factor so this difference is unlikely to affect response to teclistamab after ≥3 prior lines of treatment
- overall, MajesTEC-1 trial results are generalisable to NHS patients.

3.2.3 MajecTEC-1 trial quality assessment

The company conducted a quality assessment of the MajesTEC-1 trial using the Downs and Black checklist[25] for non-randomised trials (CS, Table 12). The company considered (CS, p60) that the MajesTEC-1 trial was of good quality and had low risk of bias. However, the EAG considers that the Downs and Black checklist[25] was not an appropriate quality assessment tool as it is intended for studies with two or more treatment groups. The EAG has therefore conducted a quality assessment exercise using the Critical Appraisal Skills Programme (CASP) checklist[27] for cohort studies. The responses to each quality item on the CASP checklist[27] are either, 'yes', 'no' or 'cannot tell'. The EAG assessment reached the same conclusion as the company assessment, i.e., that the MajesTEC-1 trial is of good methodological quality.

The EAG's assessment using the CASP checklist[27] is presented in Table 4.

Table 4 MajesTEC-1 trial quality assessment using CASP checklist

Quality assessment item	EAG assessment and comment
1. Did the study address a clearly focused issue?	Yes The MajesTEC-1 trial assessed the safety, tolerability and efficacy of teclistamab
2. Was the cohort recruited in an acceptable way?	Cannot tell The MajesTEC-1 trial had clear and pre-specified inclusion and exclusion criteria, however, recruitment methods were not reported
3. Was the exposure accurately measured to minimise bias?	Yes Exposure (intervention) was accurately measured. Teclistamab doses were clearly defined for phase I (part 1 and part 2) and phase II (part 3)
4. Was the outcome accurately measured to minimise bias?	Yes Efficacy outcomes were validated objective measures. The primary outcome, ORR, was assessed by IRC. DoR, OS, PFS and TTNT were all assessed by IRC
5a. Have the authors identified all important confounding factors?	Yes Clinical advice to the EAG is that the company identified all important confounding factors (refractory status, number of prior lines of treatment, months since diagnosis, age, ECOG PS score and cytogenetic risk)
5b. Have they taken account of the confounding factors in the design and/or analysis?	Yes Clinical advice to the EAG is that important confounding factors (refractory status, number of prior lines of treatment, months since diagnosis, age, ECOG PS score and cytogenetic risk) were considered in the company's pre-planned subgroup analyses
6a. Was the follow up of subjects complete enough?	Yes It is unclear how many patients were lost to follow up from the MajesTEC-1 trial at the 22 August 2023 DCO (CS, Figure 10). However, the EAG considers it likely that [redacted] of patients were lost to follow-up ([redacted] patients discontinued for reasons other than disease progression or death) and considers this acceptable
6b. Was the follow up of subjects long enough?	Yes At the 22 August 2023 DCO, median OS follow-up was 30.4 months (range [redacted] to [redacted] months) for the All Treated Analysis Set
7. What are the results of this study?	Patients with TCE RRMM treated with teclistamab tolerated treatment and 63.0% of patients responded to treatment. However, the study did not provide comparative evidence versus a relevant comparator
8. How precise are the results?	The results were precise and the 95% CIs were reported for the key efficacy outcomes, ORR, median DoR, median PFS and median OS
9. Do you believe the results?	Yes The median follow-up was sufficient and the results were precise
10. Can the results be applied to the local population?	Yes Clinical advice to the EAG is that, overall, MajesTEC-1 trial patients are representative of NHS patients with TCE RRMM
11. Do the results of this study fit with other available evidence?	Yes RW studies of teclistamab for TCE RRMM reported similar ORRs
12. What are the implications of this study for practice?	Cannot tell The MajesTEC-1 trial results appear to support the use of teclistamab for patients with TCE RRMM

CI=confidence interval; DCO=data cut-off; DoR=duration of response; EAG=External Assessment Group; ECOG PS=Eastern Cooperative Oncology Group performance status; IRC=Independent Review Committee; NHS=National Health Service; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; RW=real-world; TCE RRMM=triple-class exposed relapsed refractory multiple myeloma; TTNT=time to next treatment
Source: CASP checklist[27]

3.2.4 Statistical approach adopted for the analysis of the MajesTEC-1 trial

In addition to information provided in the CS, information relevant to the statistical approach taken by the company to analyse the MajesTEC-1 trial data has been extracted from the CSR September 2021 DCO[31] and CSR August 2023 DCO,[19] the trial statistical analysis plan (TSAP)[32] and the trial protocol.[30] The EAG considers that the statistical approaches adopted by the company were appropriate (see Table 5 for details).

Table 5 EAG assessment of statistical approaches used in the MajesTEC-1 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	ORR (primary endpoint), DoR, time to response, MRD negativity rate, PFS (secondary endpoints), time to next treatment, OS (exploratory endpoints) and safety analyses were carried out using data from the All Treated Analysis Set (August 2023 DCO). The All Treated Analysis Set included patients who had received at least one dose of study drug. This analysis population was pre-specified and described in the trial protocol (p124). The company has only presented results generated using data from Phase I patients who received the RP2D dose of teclistamab (n=40) and from patients in Phase II, Cohort A (n=125); the EAG considers that this is appropriate as these are the MajesTEC-1 trial patients who are relevant to this appraisal. DoR analyses were carried out using data from All Treated Analysis patients who had achieved a response (PR or better). PRO analyses were carried out using data from Phase II, Cohort A patients only
Was an appropriate sample size calculation pre-specified?	Yes	Sample size determination is described in the trial protocol (p124). In Part 2 of Phase 1, up to 40 patients were required to receive teclistamab at the proposed licensed dose determined in Part 1. In Part 3 of the MajesTEC-1 trial, it was estimated that with approximately 100 patients treated with teclistamab in Cohort A, there would be >85% power to declare the ORR is higher than 30% at the one-sided significance level of 0.025 with the assumption that ORR among those treated with teclistamab will be at least 45%. The EAG is satisfied that the sample size calculations were appropriate
Were all protocol amendments made prior to analysis?	Yes	Changes in the trial conduct are listed in the CSR (Table 2). The main protocol amendment (Amendment 8, November 2019) was the expansion of the trial to recruit patients to Cohorts B and C. Eleven protocol amendments were made before the first trial DCO (September 2021). The EAG is satisfied that the additional four amendments (CSR August 2023 DCO,[19,31] p14) have not substantially affected trial outcomes
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	**Part 2 (Phase I, dose expansion)** (protocol, p24) The primary endpoints were the occurrence and severity of AEs, SAEs and laboratory values. Key secondary endpoints were pharmacokinetic parameters and pharmacodynamic markers, response rate (including ORR), PFS and OS **Part 3 (Phase II)** (protocol, p24) The primary endpoint was ORR. Key secondary endpoints were DoR, additional response parameters as defined by IMWG criteria, PFS, OS, MRD-negative status and occurrence and severity of AEs, SAEs and laboratory values **Definitions and analysis methods**

Item	EAG assessment	Statistical approach with EAG comments
		ORR was defined as the proportion of participants who achieve PR or better (i.e., PR, VGPR, CR or sCR) according to the IMWG response criteria, during or after study intervention but before the start of subsequent anti-myeloma therapy, as assessed by the IRC (TSAP, p12). The company analysed OS and PFS data using K-M methodology. The EAG is satisfied that all primary and secondary efficacy outcomes were pre-defined and were analysed appropriately (TSAP, p13 and pp16-17)
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were assessed using the EORTC QLQ-C30, EQ-5D-5L and the PGIS instruments. PRO data were collected from the 125 patients in Phase II, Cohort A (CS, p55). The EAG is satisfied that the analysis approaches pre-specified in the TSAP (Section 5.7.6.2, p26) were appropriate
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety events were coded using the MedRA and graded using the NCI-CTCAE, v4.03, except CRS (Phase I: graded according to a CRS revised grading system; Phase II: graded according to the ASTCT grading system[33]) and ICANS events in Phase II (ICE score and ASTCT grade) (TSAP, p19). Safety data presented in the CS (Section B.2.10.2) include an overview of treatment exposure, a summary of TEAEs, most common TEAEs and CRS (an AESI)
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP (OS and MRD-negativity, p16; PROs, p25). The EAG is satisfied that the described approaches are appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	The company has presented ORR subgroup analyses (CS, Section B.2.7, pp88-90). With the exception of baseline tumour BCMA expression (which was removed as a subgroup analysis of interest in amendment 2 to the TSAP), all subgroup analyses were pre-specified in the TSAP (p28). No sensitivity analyses were presented in the CS.

AE=adverse event; AESI=adverse event of special interest; ASTCT=American Society for Transplantation and Cellular Therapy; CR=complete response; CRS=cytokine release syndrome; CS=company submission; CSR=clinical study report; DCO=data cut-off; DoR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector encephalopathy; IMWG=International Myeloma Working Group; IRC=independent review committee; K-M=Kaplan-Meier; MedRA=Medical Dictionary for Regulatory Affairs; MRD=minimal residual disease; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PGIS=Patient Global Impression of Severity; PR=partial response; PRO=patient-reported outcome; RP2D=recommended Phase II dose; sCR=stringent complete response; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan; VGPR=very good partial response
Source: CS, CSR (September 2021 DCO),[31] CSR (August 2023 DCO),[19] trial protocol,[30] TSAP,[32] and EAG comment

3.3 MajesTEC-1 trial efficacy results

MajesTEC-1 trial results for the All Treated Analysis Set (N=165) from the 22 August 2023 [redacted] DCO are summarised in Section 3.3.1 to Section 3.3.4. MajesTEC-1 trial median OS follow-up was 30.4 months (range [redacted] to [redacted] months).

3.3.1 Overall response rate

IRC-assessed ORR results (the MajesTEC-1 trial primary outcome) are presented in Table 6.

Table 6 MajesTEC-1 trial ORR results

Outcome	MajesTEC-1 trial: All Treated Analysis Set (N=165)	
	n (%)	(95% CI)
IRC-assessed ORR	104 (63.0)	[redacted]
≥VGPR (sCR + CR + VGPR)	98 (59.4)	[redacted]
≥CR (sCR + CR)	76 (46.1)	[redacted]
sCR	64 (38.8)	[redacted]
CR	12 (7.3)	[redacted]
VGPR	22 (13.3)	[redacted]
PR	6 (3.6)	[redacted]
MR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]

CI=confidence interval; CR=complete response; CS=company submission; IRC=independent review committee; MR=minimal response; ORR=overall response rate; PD=progressed disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response
Source: CS, Table 14; CSR,[19] Table 10

Approximately half (46.1%) of MajesTEC-1 trial patients achieved an IRC-assessed complete response (CR) or better to teclistamab.

3.3.2 Minimal residual disease negativity rate

Clinical advice to the EAG is that MRD negativity rate (MajesTEC-1 trial secondary outcome) is a clinically important outcome and indicates a deep clinical treatment response. In the All Treated Analysis Set, 48/165 (29.1%) patients achieved MRD negativity and [redacted] ([redacted]) patients who achieved a ≥CR also achieved MRD negativity (CS, Section B.2.6.4).

3.3.3 Duration of response

DoR results (MajesTEC-1 trial secondary outcome) are presented in Table 7.

DoR was defined as the time from the date of initial response (≥PR) to the date of first documented evidence of progressive disease (as defined by IMWG[24] criteria) or death. The median DoR for MajesTEC-1 trial patients who achieved a ≥PR was 24.0 months (95% confidence interval [CI]: 17.0 to not estimable [NE]). Median DoR was longer for patients who achieved a ≥CR (NE, 95% CI: [redacted]; CS, p69) than for patients who achieved a ≥PR.

Table 7 MajesTEC-1 trial DoR results

Outcome	MajesTEC-1 trial: All Treated Analysis Set [a] (N=104)
Median DoR (95% CI), months	24.0 (17.0 to NE)
Number of events, n (%)	[redacted]
Number of events censored, n (%)	[redacted]
DoR rate ≥6 months, % (95% CI)	90.3 [redacted]
DoR rate ≥9 months, % (95% CI)	80.6 [redacted]
DoR rate ≥12 months, % (95% CI)	69.9 [redacted]
DoR rate ≥18 months, % (95% CI)	59.2 [redacted]
DoR rate ≥24 months, % (95% CI)	50.1 [redacted]
DoR rate ≥30 months, % (95% CI)	45.0 [redacted]

[a] The denominator for median DoR is N=104 (the number of MajesTEC-1 trial patients who achieved a ≥PR, i.e., the All Treated Analysis Set ORR)
CI=confidence interval; CS=company submission; DoR=duration of response; NE=not estimable; PR=partial response; ORR=overall response rate
Source: CS, Table 15 and CS, Section B.2.6.2

3.3.4 Key survival outcomes

PFS, OS (MajesTEC-1 trial secondary outcomes) and TTNT (MajesTEC-1 trial exploratory outcome) results are presented in Table 8.

Median PFS for the All Treated Analysis Set was 11.4 months (95% CI: 8.8 to 16.4). Median PFS was not reached (95% CI: [redacted]) for patients who achieved a ≥CR (CS, Section B. 2.6.5).

TTNT was defined as the time to subsequent treatment, excluding radiotherapy or death. Median TTNT for the All Treated Analysis Set was 12.6 months (95% CI: 8.7 to 17.4) and was broadly consistent with median PFS (11.4 months, 95% CI: 8.8 to 16.4). The company presented PFS and TTNT Kaplan-Meier (K-M) curves (CS, Figure 16). Based on visual inspection of the PFS and TTNT K-M curves, the EAG agrees with the company that the TTNT and PFS K-M curves follow similar trajectories over time and overlap (Figure 1).

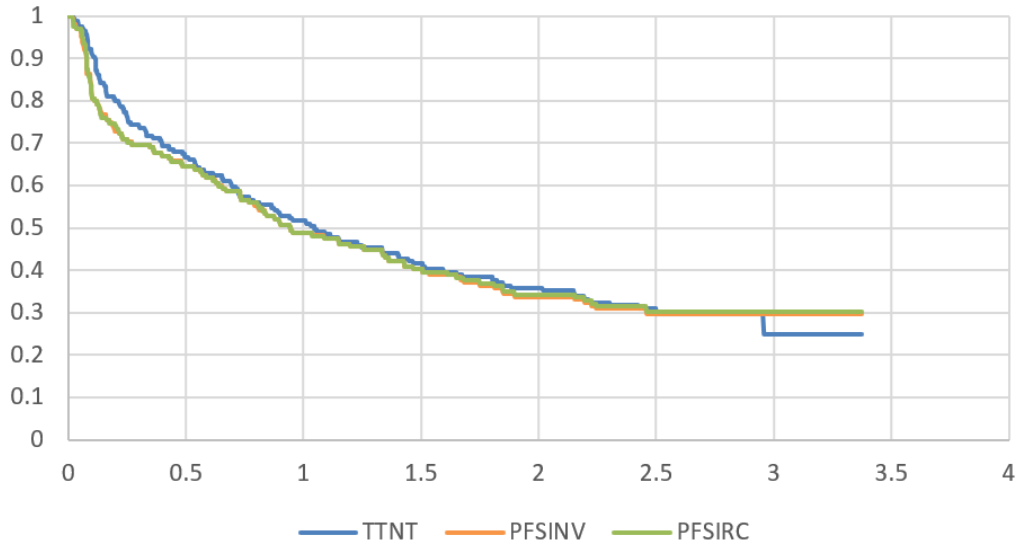

Figure 1 MajesTEC-1 trial PFS and TTNT K-M curves

CS=company submission; K-M=Kaplan-Meier; PFSINV=investigator-assessed progression-free survival; PFSIRC=independent review committee-assessed progression-free survival; TTNT=time to next treatment
Source: CS, Figure 16

Median OS for the All Treated Analysis Set was 22.2 months (95% CI: 15.1 to 29.9). Median OS was not reached (95% CI: [redacted]) for patients who achieved a ≥CR (CS, Section B.2.6.7).

The company considered that median OS may be underestimated as the MajesTEC-1 trial was ongoing during the COVID-19 pandemic; 18/94 OS events were deaths due to COVID-19. Clinical advice to the EAG is that this is a reasonable assumption. However, the UK RW TCE RRMM data were also collected over the pandemic and so median OS from the UK RW TCE RRMM study may also be underestimated.

Table 8 MajesTEC-1 trial key survival results

Outcome	MajesTEC-1 trial: All Treated Analysis Set (N=165)
Median PFS, months (95% CI)	11.4 (8.8 to 16.4)
Number of events, n (%)	107 (64.8)
Number of events censored, n (%)	58 (35.2)
PFS rate ≥6 months, % (95% CI)	64.4 [redacted]
PFS rate ≥9 months, % (95% CI)	56.6 [redacted]
PFS rate ≥12 months, % (95% CI)	48.8 [redacted]
PFS rate ≥18 months, % (95% CI)	40.3 [redacted]
PFS rate ≥24 months, % (95% CI)	34.2 [redacted]
PFS rate ≥30 months, % (95% CI)	30.1 [redacted]
Median TTNT, months (95% CI)	12.6 (8.7 to 17.4)
Number of events, n (%)	[redacted]
Median OS, months (95% CI)	22.2 (15.1 to 29.9)
Number of events, n (%)	94 (57.0%)
Number of events censored, n (%)	71 (43.0%)
OS rate ≥6 months, % (95% CI)	77.8 [redacted]
OS rate ≥9 months, % (95% CI)	74.7 [redacted]
OS rate ≥12 months, % (95% CI)	64.0 [redacted]
OS rate ≥18 months, % (95% CI)	54.6 [redacted]
OS rate ≥24 months, % (95% CI)	48.9 [redacted]
OS rate ≥30 months, % (95% CI)	41.9 [redacted]

CI=confidence interval; CS=company submission; OS=overall survival; PFS=progression-free survival; TTNT=time to next treatment
Source: CS, Table 17 and Table 18; CS, Section B.2.6.6

3.3.5 Subgroup analysis results

The company presented (CS, Section 2.7) IRC-assessed ORR subgroup analysis results for the All Treated Analysis Set patients by:

- baseline disease characteristics including ISS, revised ISS, cytogenetic risk, percentage plasma cells, tumour BCMA expression and extramedullary plasmacytomas (CS, Figure 23)
- baseline patient characteristics including age, sex, race, renal function and ECOG PS (CS, Figure 24)
- prior therapy including number of lines of prior therapy, refractory status, prior ASCT, prior allogenic stem cell transplant and type of myeloma (CS, Figure 25).

Some subgroup populations were small (e.g., for prior allogenic stem cell transplant, yes: n=[redacted]) therefore CIs were often wide. Subgroup ORRs were broadly consistent with the overall All Treated Analysis Set ORR except for ISS Stage III and extramedullary plasmacytomas ≥1; these subgroup ORRs were statistically significantly lower than the overall All Treated Analysis Set ORR.

3.4 TCE RRMM real-world data

The company reported (CS, p36, p64 and p115) ORR results from two RW retrospective studies of patients with TCE RRMM treated with teclistamab (the Dima study[20] and the Riedhammer study[21]). These two RW studies[20,21] were not identified by the company SLR because they were published after the most recent search date (October 2023).

In the absence of PomDex clinical trial evidence for patients with TCE RRMM (see Section 3.1.1), the company presented RW data from patients treated with PomDex in the UK RW TCE RRMM study.

3.4.1 Characteristics of the teclistamab real-world studies

The Dima study[20] was a retrospective cohort study of patients with TCE RRMM (N=106) treated with teclistamab in five US academic centres from August 2022 to August 2023 via an expanded access program or in line with the Food and Drug Administration marketing authorisation (approved October 2022).[34] The outcomes assessed were PFS, OS, ORR and AEs (specifically, cytokine release syndrome [CRS], immune effector cell-associated neurotoxicity syndrome [ICANS] and infection rates). HRQoL data were not collected.

The Riedhammer study[21] was a retrospective cohort study of patients with TCE RRMM (N=123) treated with teclistamab across 18 German centres from July 2022 to October 2023 in line with the teclistamab EMA marketing authorisation.[8] The outcomes assessed were PFS, OS, ORR, DoR and AEs. HRQoL data were not collected.

3.4.2 Characteristics of the PomDex UK RW TCE RRMM study

The UK RW TCE RRMM study is a registry study using NHS England (NHSE) cancer and linked datasets that are available through NCRAS.[22] In this study, patients were followed-up from initiation of their current line of treatment until death, relocation outside of England or until DCO.

All UK RW TCE RRMM study data included in this report are from the CS, Section 2.9 and Appendix D.2.3.

3.4.3 Characteristics of study patients

The EAG has compared the baseline characteristics of the MajesTEC-1 trial All Treated Analysis Set population, the two teclistamab RW study populations[20,21] and the UK RW TCE RRMM study population (Table 9).

Table 9 Baseline characteristics of MajecTEC-1 trial and the two real-world teclistamab study patients

Characteristic	Teclistamab			PomDex	Study population most representative of NHS patients (clinical advice to the EAG)
	MajesTEC-1 All Treated Analysis Set (N=165)	Dima US retrospective study[20] (N=106)	Riedhammer German retrospective study[21] (N=123)	UK RW TCE RRMM study PomDex ECOG PS 0/1 (N=645)	
Age, median (range), years	64.0 (33 to 84)	66.5 (35 to 87)	67.0 (35 to 87)	72.7 (65.4 to 78.0)	UK RW TCE RRMM study
Male, n (%)	96 (58.2)	49 (46)	70 (56.9)	368 (57.1)	MajesTEC-1 trial, Riedhammer study[21] and UK RW TCE RRMM study
Time since diagnosis, median (range) years	6.0 (0.8 to 22.7)	5.4 (0.5 to 20)[a]	6.5 (0.5 to 18.7)	4.4 (3.2 to 5.8)[b]	MajesTEC-1 trial and Riedhammer study[21]
Previous lines of treatment, median (range)	5 (2 to 14)	6 (4 to 17)	6 (3 to 14)	4 (3 to 7)	UK RW TCE RRMM study
Extramedullary disease, n/N (%)	28/165 (17.0)	45/106 (42)	43/119 (36.1)	NR	Dima study[20] and Riedhammer study[21]
ISS, n/N (%)[c]					
I	85/162 (52.5)	NR	25/92 (27.1)	58/645 (9.0)	Riedhammer study[21] and UK RW TCE RRMM study
II	57/162 (35.2)	NR	35/92 (38.0)	73/645 (11.3)	
III	20/162 (12.3)	NR	31/92 (33.7)	85/645 (13.2)	
Unknown	NR	NR	NR	429/645 (66.5)	
ECOG PS					
0	55 (33.3)	71 (67)[d]	NR	133 (20.6)	Dima study[20]
1	[redacted]		NR	512 (79.4)	
2 to 4	[redacted]	35 (33)	NR	N/A	
High risk cytogenetic profile, n/N (%)	[redacted]	56/95 (59)	39/106 (36.8)	NR	Dima study[20] and Riedhammer study[21]
Prior ASCT, n (%)	135 (81.8%)	61 (58)	NR	225 (34.9)	Dima study[20] and UK RW TCE RRMM study
Prior anti-BCMA treatment, n (%)	0 (0)	56 (53)	45 (37.4)	NR[e]	MajesTEC-1 trial and UK RW TCE RRMM study

[a] Median time since diagnosis was reported in months and was converted to years by dividing by 12
[b] Median time since diagnosis was reported in days and was converted to years by dividing by 365
[c] For the UK RW TCE RRMM study, ISS stage was only assessed at diagnosis
[d] In Dima 2023, the number of patients with ECOG PS 0 and ECOG PS 1 was not reported separately
[e] The EAG considers that UK RW TCE RRMM cohort study patients will likely be anti-BCMA treatment-naïve because there are no routinely available NICE-recommended anti-BCMA treatments
ASCT=autologous stem cell transplantation; BCMA=B-cell maturation antigen; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ISS=International Staging System; NHS=National Health Service; NR=not reported; PomDex=pomalidomide plus low-dose dexamethasone; RW=real-world

Source: CS, Table 7, Table 8 and Table 25; CS, Appendix D.2.3, Table 14; Dima 2023;[20] Riedhammer 2024[21]

Clinical trial evidence Teclistamab (clinical trial evidence) versus teclistamab (real-world evidence)

Compared to the MajesTEC-1 trial All Treated Analysis Set population characteristics, the Dima study[20] and Riedhammer study[21] populations included a higher proportion of patients who had:

- extramedullary disease
- ISS III RRMM (the Riedhammer study[21] only; ISS staging was not reported in the Dima study)[20]
- RRMM with high risk cytogenetics
- triple-class and/or penta-class RRMM
- ECOG PS ≥2 (the Dima study[20] only; ECOG PS was not reported in the Riedhammer study)[21]
- prior anti-BCMA treatment.

Clinical advice to the EAG is that the Dima study[20] and the Riedhammer study[21] populations were less fit and had a worse prognosis than the MajesTEC-1 trial All Treated Analysis Set population and are therefore more representative of NHS patients with TCE RRMM. However, the Dima study[20] and the Riedhammer study[21] populations were more heavily pre-treated than the MajesTEC-1 trial All Treated Analysis Set population and NHS patients with TCE RRMM.

Teclistamab (clinical trial evidence) versus PomDex (real-world evidence)

In total, 896 patients in the UK RW TCE RRMM study received PomDex. To align with the MajesTEC-1 trial inclusion criteria, the company only presented data from UK RW TCE RRMM study patients with an ECOG PS 0 or 1 who received PomDex (n=645), hereafter referred to as the PomDex cohort. The company imputed missing ECOG PS values for 214 of the 896 patients treated with PomDex. The EAG considers that the methods used by the company to perform imputations (described in CS, Appendix D, Section 2.4) were appropriate.

The UK RW TCE RRMM study PomDex cohort, when compared to the MajesTEC-1 trial All Treated Analysis Set population:

- were on average older (median age: 72.7 years versus 64.0 years)
- had a shorter median time from diagnosis to first dose of treatment (4.4 years versus 6.0 years)
- had, on average, received fewer previous line of therapy (median 4 versus 5)
- a lower proportion had triple-class refractory disease (49.6% versus 77.6%) and/or penta-class refractory disease (4.5% versus 30.3%)
- a lower proportion had received prior ASCT (34.9% versus 81.8%).

Clinical advice to the EAG

Clinical advice to the EAG is that, overall, the UK RW TCE RRMM study PomDex cohort is more representative of NHS patients with TCE RRMM than the MajesTEC-1 trial, the Dima study[20] and the Riedhammer study[21] populations because:

- the data are specific to the UK
- the proportion of patients who received prior ASCT is similar to the proportion of NHS patients who receive prior ASCT, although prior ASCT is not a prognostic factor
- the median number of prior lines of treatment is similar to the median number of prior lines of treatment received by NHS patients.

However, clinical advice to the EAG is that the UK RW TCE RRMM study PomDex cohort is not wholly representative of NHS patients as:

- median time from diagnosis to first dose of PomDex in the UK RW TCE RRMM study was shorter than would be expected for NHS patients with TCE RRMM
- the UK RW TCE RRMM study included patients with TCE RRMM who were diagnosed with MM over ten years ago (January 2013 to 31 December 2021) and since then NHS clinical practice has evolved.

3.4.4 Real-world evidence efficacy results

Key efficacy results from the MajesTEC-1 All Treated Analysis Set population, the Dima study,[20] the Riedhammer study[21] and the UK RW TCE RRMM study are presented in Table 10.

Table 10 MajesTec-1 trial and real-world teclistamab studies key efficacy outcomes

Outcome	Teclistamab			PomDex
	MajesTEC-1 All Treated Analysis Set (N=165)	Dima 2023[20] US retrospective study (N=106)	Riedhammer 2024[21] German retrospective study (N=123)	UK RW TCE RRMM study PomDex ECOG PS 0/1 (N=645)
Median follow-up, months	30.4[a]	3.8	5.5	26.0
ORR (95% CI)	63.0 [redacted]	66 (NR)	59.3 (NR)	NR
≥CR (95% CI)	46.1 [redacted]	29 (NR)	NR	NR
Median PFS, months (95% CI)	11.4 (8.8 to 16.4)	5.4 (3.4 to NE)	8.7 (NR)	NR
Median TTNT, months (95% CI)	12.6 (8.7 to 17.4)	NR	NR	7.03 (6.54 to 7.81)
Median OS, months (95% CI)	22.2 (15.1 to 29.9)	NE	NE	9.78 (8.64 to 10.82)

[a] Median OS follow-up; median PFS follow-up was [redacted]
CI=confidence interval; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ISS=International Staging System; NE=not estimable; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; TCE RRMM=triple-class exposed relapsed refractory multiple myeloma; TTNT=time to next treatment
Source: CS, Table 14, Table 17 and Table 18; Dima 2023;[20] Riedhammer 2024[21]

Teclistamab (clinical trial evidence) versus teclistamab (real-world evidence) results

Dima study[20] (70/106 [66.0%] patients) and Riedhammer study[21] (73/123 [59.3%] patients) ORR results were consistent with the MajesTEC-1 trial ORR result. Only the Dima study[20] reported ≥CR rate. The ≥CR rate was substantially lower in the Dima study[20] than in the MajesTEC-1 trial. Median PFS was shorter in the Dima study[20] and the Riedhammer study[21] than in the MajesTEC-1 trial; however, median follow-up was also substantially shorter in the Dima study[20] and the Riedhammer study[21] than in the MajesTEC-1 trial. Median OS was not reached in the Dima study[20] or in the Riedhammer study.[21]

Teclistamab (clinical trial evidence) versus PomDex (real-world evidence) results

Median TTNT and median OS were substantially shorter in the UK TCE RW cohort study (PomDex) than in the MajesTEC-1 trial (teclistamab).

3.5 EAG summary and critique of the indirect evidence

The company identified that PomDex was the only relevant comparator to teclistamab for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb and whose disease progressed on the last treatment received (see Section 2.4.4). As the company's SLR did not identify any head-to-head trials investigating the efficacy of teclistamab versus PomDex, the company conducted ITCs to estimate the comparative efficacy of teclistamab versus PomDex for the relevant patient population.

3.5.1 Studies included in the indirect comparisons

In the absence of relevant trial data, the company used PomDex data from the UK RW TCE RRMM study. To align with the MajesTEC-1 trial inclusion criteria, the ITCs only used data from UK RW TCE RRMM study PomDex cohort (n=645; i.e., patients with an ECOG PS of 0 or 1 who received PomDex). The most recent DCO was March 2023 (median follow-up time for the PomDex cohort was 26 months); these 2023 data were used to inform the company's OS and TTNT (a proxy for PFS) ITCs.

A summary of the UK RW TCE RRMM study methodology is available in Table 11.

Table 11 Summary of the UK RW TCE RRMM study methodology

Study design	A descriptive, non-interventional, cohort study designed to retrospectively track the treatment pathway and health outcomes of patients with MM using routine healthcare data
Data sources	Several linked datasets are available through the NCRAS[22] at NHSE: • NCRD[22] provides a register of primary cancer diagnoses in England from 1971 to 2021 • HES database[35] provides national coverage of secondary care, including inpatient, outpatient, and accident and emergency admissions • SACT[36] contains cancer-specific systemic treatment information for NHS patients in England
Study populations	General eligibility criteria Included patients had ≥1 primary MM diagnosis, defined as ICD-O-3 morphology code 9732, between 1 January 2013 and 31 December 2021 in England and were aged ≥18 years at diagnosis. It was further required that patients received ≥3 LOTs that included a PI, an IMiD, and an anti-CD38 mAb, either alone or in combination. Patients were excluded if their MM diagnosis was identified via death certificate only, as the lack of follow-up data negates any ability to calculate treatment or survival. They were also excluded if there was no linkage to a SACT record for an ICD-10-C90 tumour, where treatment was after or up to 1 month before the first cohort-relevant diagnosis. The study included an 'overall cohort' and to be eligible for inclusion, all patients must have initiated a new line of systemic anti-cancer therapy after meeting the general eligibility criteria, i.e., after becoming TCE following three or more prior LOTs. The index LOT was the first line of systemic anti-cancer therapy that followed the patient meeting all eligibility criteria. CDF treatment data were not available in this dataset. An additional cohort, PomDex (ECOG PS restricted 0 to1), was defined specifically to inform the NICE appraisal of teclistamab. Patients must have initiated a new line of PomDex therapy after meeting the general eligibility criteria and have an ECOG score at baseline of 0 or 1. The index LOT was the first PomDex LOT that the patient received after meeting all eligibility criteria (this may or may not be the first LOT received after becoming eligible). The overall cohort and study methodology are further described by Elsada 2021[28]
Time zero and follow-up	T^0 was defined as the start of the index LOT. Patients were followed from T^0 to the earliest of death, embarkation (relocation outside England), or March 2023.
Outcomes	OS and TTNT (proxy for PFS due to absent PFS data) were calculated using the K-M estimator: • OS failure was defined as death from any cause between T^0 and the end of follow-up • TTNT was the earliest of either a change in LOT or death within the study period For both outcomes, patients were censored on March 2023 if alive at the end of the study period, or else on the date of embarkation if they left England during the study period
Subsequent therapy	Patient counts and regimen descriptions were generated for patients who went on to receive one or more subsequent LOT after their index LOT within the study period

CDF=Cancer Drugs Fund; CD38=cluster of differentiation 38; CS=company submission; HES=hospital episode statistics; ECOG PS=Eastern Cooperative Oncology Group performance status; ICD-O-3=International Classification of Diseases for Oncology, code 3; ICD-10-C90=International Classification of Diseases, Tenth Revision, code C90; IMiD=immunomodulatory agent; K-M=Kaplan-Meier; LOT=line of treatment; mAb=monoclonal antibody; MM=multiple myeloma; NCRAS=National Cancer Registration and Analysis Service; NCRD=National Cancer Registration Dataset; NHS=National Health Service; NHSE=National Health Service England; NICE=National Institute for Health and Care Excellence; OS=overall survival; PFS=progression-free survival; PI=proteasome inhibitor; PomDex=pomalidomide plus low-dose dexamethasone; RRMM=relapsed or refractory multiple myeloma; RW=real-world; SACT=Systemic Anti-Cancer Therapy dataset; T^0=time zero; TCE=triple-class exposed; TTNT=time to next treatment; UK=United Kingdom
Source: CS, Table 22

3.5.2 UK RW TCE RRMM study quality assessment

The company conducted a quality assessment of the UK RW TCE RRMM study using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool[26] (CS, Appendix

D.2.6, Table 19 to Table 23). The EAG considers that the ROBINS-I tool[26] was appropriate because the UK RW TCE RRMM study included multiple interventions.

Overall, the EAG agrees with the company's assessment of the review question (CS, Appendix 2.6, Table 19), the target randomised trial (CS, Appendix D.2.6, Table 20), the consideration of confounders (CS, Appendix D.2.6, Table 21) and co-interventions (CS, Appendix D.2.6, Table 22).

The EAG agrees with the company that, in line with the ROBINS-I tool,[26] the UK RW TCE RRMM study has serious risk of confounding bias as although confounders were appropriately measured and reported, no confounders (not even confounders that were prognostic factors) were adjusted for. However, the EAG notes that the company applied additional selection criteria (CS, Table 23) to restrict the overall UK RW TCE RRMM study population to patients who were relevant to this appraisal; this approach controlled for one prognostic factor (i.e., patients with ECOG PS 0 or 1 who received PomDex). The ROBINS-I tool guidance[37] acknowledges that non-randomised studies rarely have low risk of confounding bias.

When using the ROBINS-I tool,[26] if a study is judged to be at serious risk of bias ≥1 domain (but not at critical risk of bias in any domain), the study should be assessed as having serious overall risk of bias. The EAG and the company therefore agree that the UK RW TCE RRMM study has serious overall risk of bias (see Table 12 for a summary of the company's and EAG's assessment of the UK RW TCE RRMM study and see Appendix 2, Section 8.2, Table 38 for the company's and EAG's full quality assessment of the UK RW TCE RRMM study).

ROBINS-I tool guidance[37] states that only studies with critical overall risk of bias are too problematic to provide any useful evidence. The EAG therefore considers that it is reasonable to use evidence from the UK RW TCE RRMM study to inform ITCs, despite the study having serious overall risk of bias.

Table 12 Summary of UK RW TCE RRMM study quality assessment using the ROBINS-I tool

Signalling question[a]	Company comment	Company assessment	EAG assessment for median TTNT[b]	EAG assessment for median OS[b]
Bias due to confounding	Confounding domains were generally reliably measured, but were not controlled for	Serious	Serious	Serious
Bias in selection of participants into the study	All eligible participants were included in the study, and start of follow up coincided with start of intervention	Low	Low	Low
Bias in classification of interventions study	Intervention status is well-defined and classified upon input into database (i.e., independently of those with knowledge of treatment outcomes)	Low	Low	Low
Bias due to deviations from intended interventions	Any potential deviations from intervention would reflect usual practice	Low	Low	Low
Bias due to missing data	All patients had outcome data reported and no patients were excluded from the analysis based on missing data	Low	Low	Low
Bias in measurement of outcomes	Both outcomes involve negligible assessor judgement so risk of bias is expected to be low	Low	Low	Low
Bias in selection of the reported result	Outcome measurements and analyses clearly pre-specified. The study did not involve conducting multiple outcome measurements and analyses so risk of selective reporting unlikely	Low	Low	Low
Overall risk of bias judgement	Risk of bias judged to be low for 6/7 domains of bias. Only risk of bias due to confounding was judged to be serious, although this is expected given that the UK RW TCE RRMM study is non-randomised	Serious	Serious	Serious

[a] The responses to each signally question on the ROBINS-I tool[26] are either, 'yes', 'probably yes', 'probably no', 'no' or 'no information'.
[b] The ROBINS-I tool[26] step 3 to step 6 of the assessment should be completed separately for each key outcome
CS=company submission; EAG=External Assessment group; 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
Source: CS, Appendix D.2.6, Table 2

3.5.3 Analysis methods

Full details of company ITC methods are provided in the CS (Appendix D).

ITC methodology

As noted by the company (CS, p95), naïve comparisons of non-randomised data are typically biased due to confounding arising from imbalances between study populations for prognostic factors of interest. When comparative IPD are available, various methods can be used to adjust for confounding variables. In the company base case, adjustments for confounding

variables were made using the inverse probability of treatment weighting (IPTW) method as this approach leverages information for all patients. Using estimand-specific weighting formulas (CS, Appendix D), the IPTW method utilises the propensity score to derive weights for each patient so that the baseline characteristics of patients in the treated (teclistimab) and untreated (PomDex) groups are balanced after weighting. Company sensitivity analyses were carried out to explore the effect of using other adjustment methods, including multivariable regression and PS matching.

Weighting approaches

Multiple weighting methods can be used when implementing the IPTW method. The company considered (and clinical advice to the EAG agrees) that, compared with the MajesTEC-1 trial All Treated Analysis Set population, the UK RW TCE RRMM study PomDex cohort is more representative of NHS patients and that the average treatment effect for the control (ATC) weighting approach was the most appropriate adjustment method; this approach allows MajesTEC-1 trial cohort characteristics to be re-weighted to mimic the UK RW TCE RRMM study PomDex cohort. The company applied a 'scaled weights for average treatment effect for the control (sATC)' approach to ensure that the sample size of the weighted MajesTEC-1 data set matched the original sample size of the unweighted MajesTEC-1 data set. Sensitivity analyses were carried out to explore the effect of using alternative weightings, including average treatment effect for the treated population (ATT), average effect on the overlap population (ATO) and average treatment effect (ATE).

Identification of co-variates

Relevant co-variates were identified in consultation with clinical experts; details of the company's methodology are provided in the CS (Appendix D, Section 2.4).

In total, 17 potential covariates were identified, and of these, five were deemed to be priority prognostic factors (Table 13). However, in addition to deprioritising sex as a variable to allow the K-3 anonymity check to be passed, the company considered that the UK RW TCE RRMM study only had sufficient IPD available to facilitate adjustment for six variables; only one of these six variables (i.e., refractory status) was considered a priority factor. The company's justifications for excluding individual variables are presented in the CS (p97).

Table 13 Identification and ranking of ITC prognostic factors

Rank	Factor	Available in UK RW TCE RRMM study
Priority	**Refractory status**	**Yes**
Priority	**Cytogenetic profile**	No
Priority	**ISS stage**	No
Priority	**Time to progress on last regimen**	No
Priority	**Extramedullary plasmacytoma**	No
Non-priority	Number of prior LOTs	**Yes**
Non-priority	Years since MM diagnosis	**Yes**
Non-priority	Age	**Yes**
Non-priority	Haemoglobin	No
Non-priority	LDH levels	No
Non-priority	Prior stem cell transplant	**Yes**
Non-priority	ECOG PS	**Yes**
Non-priority	Race	No
Non-priority	Sex	No
Non-priority	Type of multiple myeloma	No
Non-priority	Creatinine levels	No
Non-priority	Average duration of prior lines of treatment	No

CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ISS=International Staging System; ITC=indirect treatment comparison; LDH=lactate dehydrogenase; LOT=line of treatment; RRMM=relapsed, refractory multiple myeloma
Source: CS, Table 24

Assessment of overlap

The extent of overlap of the six UK RW TCE RRMM study variables was evaluated before and after adjustment. Standardised mean differences (SMDs) were used to evaluate the differences for each variable included in the analysis; an SMD >0.2 was considered to indicate a substantial difference in the distribution of the variable between the MajesTEC-1 trial All Treated Analysis Set population and the UK RW TCE RRMM study PomDex cohort.

Before the 6-variable adjustment, SMDs were large (>0.2) for all variables (Table 14). SMDs showed that MajesTEC-1 trial patients were, on average, younger, had a longer time since diagnosis, had a higher number of prior treatments, were more refractory and were more likely to have received ASCT than patients in the UK RW TCE RRMM study PomDex cohort.

Table 14 SMD for differences between prognostic factors in the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort

	Before adjustment		
	Teclistamab	**PomDex**	**SMD**
N	165	645	-
Refractory status, n (%)			
≤double-refractory	[redacted]	325 (50.4)	[redacted]
Triple/quad-refractory	[redacted]	291 (45.1)	
≥penta-refractory	50 (30.3)	29 (4.5)	
Number of prior lines of treatment, n (%)			
≤4	[redacted]	534 (82.8)	[redacted]
≥5	[redacted]	111 (17.2)	
ECOG PS, n (%)			
0	[redacted]	133 (20.6)	[redacted]
1	[redacted]	512 (79.4)	
Age, n (%)			
<65	[redacted]	154 (23.9)	[redacted]
≥65	[redacted]	491 (76.1)	
Prior ASCT, n (%)			
Yes	135 (81.8)	225 (34.9)	[redacted]
No	30 (18.2)	420 (65.1)	
Time (months) since diagnosis, n (%)			
1–47	[redacted]	268 (41.6)	[redacted]
48+	[redacted]	377 (58.4)	

ASCT=autologous stem cell transplantation; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; PomDex=pomalidomide plus low-dose dexamethasone; SMD=standardised mean difference
Source: CS, Table 27

Following the 6-variable adjustment, three of the six variables (ECOG PS, age, and prior ASCT) had SMDs above the threshold of 0.2, indicating that differences in baseline characteristics between studies persisted post-adjustment. The EAG has not presented the post-adjustment SMDs due to concerns regarding the appropriateness of the IPTW adjustment method (Section 3.5.5 of this EAG report). Four clinical experts identified ASCT as one of the lowest priority prognostic variables. The company compared the prognostic impact of ASCT on OS and TTNT and found that there were no statistically significant differences in OS or TTNT between patients who had or had not had an ASCT (CS, Table 26); this result held for both the MajesTEC-1 trial All Treated Analysis Set population and the PomDex cohort. The company concluded that these findings, along with clinical advice to the company that ASCT is highly correlated with age, supported the appropriateness of removing ASCT as an adjustment factor in the base case analysis. Therefore, prior ASCT was removed from the weighting process and the populations were re-weighted using a 5-variable

adjustment. The company considered that adjusting for five variables (refractory status, number of prior lines of treatment, ECOG PS, age and months since diagnosis) represented the most appropriate approach since overlap between the populations improved notably versus adjusting for six variables; only one variable (prior ASCT) had a SMD > 0.2 following the 5-variable adjustment. Again, the EAG has not presented the post-adjustment SMDs due to concerns regarding the appropriateness of the IPTW adjustment method (Section 3.5.5 of this EAG report). The company highlighted that the 5-variable adjustment approach generated more conservative efficacy results (Table 15) for teclistamab than the 6-variable adjustment approach.

3.5.4 Company ITC results

Base case results

Company base case OS and TTNT ITC results are presented in Table 15. OS and TTNT K-M curves are presented in the CS (Figure 31 and Figure 32). The reported hazard ratios (HRs) indicated a statistically significant treatment effect in favour of teclistamab over PomDex for both OS and TTNT.

Table 15 Company base case overall survival and time to next treatment indirect treatment comparison results

	Teclistamab (post sATC weighting) ESS=[redacted]	**PomDex N=645**
OS		
Median OS	22.21 months	9.78 months
Difference between teclistamab and PomDex median OS	12.43 months (127.1% increase)	
HR (95% CI)	0.52 (0.36 to 0.74)	
TTNT		
Median TTNT	12.39 months	7.03 months
Difference between teclistamab and PomDex median OS	5.36 months (76.2% increase)	
HR (95% CI)	0.56 (0.40 to 0.79)	

CI=confidence interval; CS=company submission; ESS=effective sample size; HR=hazard ratio; PomDex=pomalidomide plus low-dose dexamethasone; OS=overall survival; sATC=stabilised average treatment effect for the control; TTNT=time to next treatment
Source: CS, p105

As Cox PH models were used to estimate HRs and 95% CIs, the company assessed the validity of the PH assumption for each ITC. The Cox PH model is only an appropriate method if the PH assumption holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The company considered log-cumulative hazard plots, Schoenfeld residual plots and the global Schoenfeld residuals test of proportional

hazards to assess the PH assumption (CS, Appendix N, Figure 15 to Figure 18). The company concluded that the PH assumption was violated for both the OS and TNT ITCs. The company did not perform any additional analyses that did not rely on the PH assumption being valid.

Sensitivity analysis results

The company carried out 12 OS and 12 TTNT sensitivity analyses (results provided in the CS, Figure 33 and Figure 34, respectively). These analyses explored the impact of using alternative ITC methodologies and different numbers of adjustment variables (n=5 or n=6) on ITC results. The sensitivity analysis results showed that treatment with teclistamab was statistically significantly better than PomDex across all presented analyses, with the majority of OS and TTNT HRs <[redacted].

3.5.5 EAG critique of company indirect comparisons

Considering the company's assessment of overlap prior to population adjustment, the EAG notes that SMDs were >0.25 for all six adjustment variables, which signals problems with overlap between populations.[38] An important issue arises if there are problems with overlap, i.e., predicted propensity scores may be close to zero, leading to excessively large weights (as weights were calculated by taking the inverse of propensity scores). The IPTW method may therefore be unstable, and the estimated treatment effects may be biased.

Histograms of propensity scores may be used to further assess the extent of overlap between populations. The company presents the distribution of propensity scores (prior to population adjustment) in the CS (CS, Figure 27). The company also presented histograms of propensity scores post adjustment (6-variable adjustment, CS, Figure 28; 5-variable adjustment, CS, Figure 30), stating that differences in baseline characteristics between studies persisted following the 6-variable adjustment (CS, pp100-101), but that overlap between the two populations improved notably following the 5-variable adjustment (CS, p102).

When problems with overlap have been identified, NICE Decision Support Unit Technical Support Document (DSU TSD) guidance is that trimming of the sample, or matching, should be performed to improve overlap (Figure 3, NICE DSU TSD 17[38]); the company's base case analyses did not employ either of these methods. Furthermore, the EAG considers that, of the 12 OS sensitivity analyses presented by the company, only two analyses, referred to as "PS matching (c=0.20) – 5 vars" and "PS matching (c=20) – 6 vars" (CS, Figure 33), were likely to have employed methods to improve overlap between the teclistamab and PomDex populations. As part of the company's factual accuracy check (FAC), the company provided methodological details for the propensity score matching sensitivity analyses and the IPTW ATO approach (company FAC, Appendix 4). The company also provided results from

additional sensitivity analyses which used the ATC truncation and ATC trimming approach (company FAC, Appendix 3). Results from these sensitivity analyses (company FAC, Appendix 3, Figure 7 and Figure 8) were similar to those reported in the company base case analysis (CS, Table 28).

The company was also unable to adjust for four priority prognostic factors identified by the company (cytogenetic profile, ISS stage, time to progress on last regimen, extramedullary plasmacytoma). Clinical advice to the EAG is that cytogenetic profile is the most important factor; patients with high-risk cytogenetic profiles are likely to experience worse treatment outcomes than patients with standard-risk cytogenetic profiles. Cytogenetic profile data are not routinely collected in NHS clinical practice and so were not available for the UK RW TCE RRMM study PomDex cohort. Clinical advice to the EAG is that there may be a higher proportion of patients with high-risk cytogenetic profiles in NHS clinical practice than observed in the MajesTEC-1 trial ([redacted]). As the cytogenetic profile imbalance between study cohorts is unknown, the impact of not adjusting for this prognostic factor is also not known.

Furthermore, the company concluded that the PH assumption was violated for both the OS and TTNT ITCs. The EAG considers that the violation of PH introduces further uncertainty regarding the accuracy of reported HRs for the comparison of teclistamab versus PomDex. The EAG highlights that the company did not assess the PH assumption for any of the sensitivity analyses or perform any additional analyses that did not rely on the PH assumption.

Finally, the EAG notes that the company assigned weights to MajesTEC-1 trial patient data so that the baseline characteristics of the weighted MajesTEC-1 trial patients matched the baseline characteristics of the UK RW TCE RCMM study PomDex cohort (ATC weighting approach). The company selected this weighting approach as clinical advice to the company was that the UK RW TCE RRMM study population was more representative of NHS patients than the MajesTEC-1 trial All Treated Analysis Set population; clinical advice to the EAG agrees with the company's view (see Section 3.4.3). The EAG therefore considers that the company's use of ATC weighting in the base case analysis was appropriate. However, clinical advice to the EAG was that the MajesTEC-1 trial may be more reflective of current NHS clinical practice than the UK RW TCE RRMM study as time from diagnosis to first dose of treatment was longer, and also because the UK RW TCE RRMM study PomDex cohort includes patients who were diagnosed with MM over 10 years ago (see Section 3.4.3). Therefore, the EAG considers the company's use of alternative weighting approaches (ATT, ATE, ATO) in sensitivity analyses was well-justified. Results from these sensitivity analyses were similar to those reported in the company base case analysis.

Overall, the EAG considers that the company ITCs are methodologically flawed and results may be unreliable.

3.6 Patient reported outcomes from the MajesTEC-1 trial

HRQoL data (secondary outcome) were collected from MajesTEC-1 trial Cohort A patients (n=125). HRQoL data were collected at baseline and then every other cycle until end of treatment. For the post-treatment follow-up phase, HRQoL data were collected every 16 weeks (±2 weeks) from disease progression or the end of treatment visit until the end of study, patient death, loss to follow-up or withdrawn consent, dependent on which occurred first. HRQoL data were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC QLQ-C30), the EuroQol Five-Dimensions Five-Level (EQ-5D-5L) questionnaire and the Patient Global Impressions-Severity (PGI-S) questionnaire.

3.6.1 EORTC QLQ-C30

Baseline EORTC QLQ-C30 data were available for [redacted]/125 ([redacted]) Cohort A patients. Mean global health status (GHS) score at baseline was [redacted] (standard deviation [SD]: [redacted]; CSR August 2023 DCO,[19] Table 15).

EORTC QLQ-C30 data were available for [redacted] patients who had completed a full EORTC-QLQ-C30 assessment at baseline and at Cycle 12. Approximately [redacted] of patients reported [redacted] for GHS ([redacted], [redacted]), fatigue ([redacted], [redacted]) and pain ([redacted], [redacted]) subscale scores at Cycle 12. All mean subscale scores [redacted] from baseline to Cycle 12, except for nausea and vomiting scores which [redacted] (CSR August 2023 DCO,[19] Table tproqlq02rp2d)

3.6.2 EQ-5D-5L

Baseline EQ-5D-5L data were available for [redacted]/125 ([redacted]) Cohort A patients. At baseline, mean utility score was [redacted] (SD: [redacted]; CSR August 2023 DCO,[19] Table tproeq02rp2d) and mean visual analogue scale (VAS) score was [redacted] (SD: [redacted]).

EQ-5D-5L data were available for [redacted] patients who had completed a full EORTC-QLQ-C30 assessment at baseline and at Cycle 12. Mean VAS score [redacted] by [redacted] (SD: [redacted]) and mean utility score [redacted] by [redacted] (SD: [redacted]) from baseline to Cycle 12 (CSR August 2023 DCO,[19] Table tproeq02rp2d). Median time to [redacted] in utility score and VAS score was [redacted] months and [redacted] months, respectively (CSR August 2023 DCO,[19] Table tproeq03rp2d).

3.6.3 PGI-S

Baseline PGI-S data were available for [redacted]/125 ([redacted]) Cohort A patients. At baseline, [redacted] ([redacted]) and [redacted] ([redacted]) Cohort A patients reported their disease severity as none or mild, respectively.

PGI-S data were available for [redacted] patients who had completed a full EORTC-QLQ-C30 assessment at baseline and at Cycle 12. At Cycle 12, the proportion of patients who rated disease severity as [redacted] and the proportion of patients who rated their disease severity as [redacted] (CS, Figure 22). The largest differences were observed in the proportion of patients who reported their disease severity as [redacted] at Cycle 12 compared to baseline (CSR August 2023 DCO,[19] Table tpropgis02rp2d):

- the proportion of patients who reported their disease severity as [redacted] at Cycle 12 ([redacted] patients, [redacted]) than at baseline ([redacted] patients, [redacted])
- the proportion of patients who reported their disease severity as [redacted] at Cycle 12 ([redacted] patients, [redacted]) than at baseline ([redacted], [redacted]).

3.7 Safety and tolerability results from the MajesTEC-1 trial

MajesTEC-1 trial safety results for the All Treated Analysis Set (N=165) from the 22 August 2023 final DCO are summarised in Section 3.7.1 to Section 3.7.3. Median duration of treatment was [redacted] months (range: [redacted] to [redacted] months) and median teclistamab dose intensity across all treatment cycles was [redacted]ug/kg/week (range: [redacted] to [redacted]ug/kg/week). The median number of doses received was [redacted] (range: [redacted] to [redacted]) and 65/165 (39.3%) patients switched from Q1W to Q2W dosing. Only 8/165 (4.8%) patients discontinued treatment due to an TEAE.

3.7.1 Treatment-emergent adverse events

[redacted] patients experienced ≥1 treatment-emergent adverse event (TEAE) of any grade and [redacted]/165 ([redacted]) patients experienced ≥1 (any grade) treatment-related adverse event (TRAE). The most common (any grade) TEAEs (CS, Table 31) were:

- CRS (119/165 [72.1%] patients)
- neutropenia (118/165 [71.5%] patients)
- anaemia (91/165 [55.2%] patients).

[redacted]/165 ([redacted]) patients experienced ≥1 serious TEAE; [redacted]/165 ([redacted]) patients experienced ≥1 Grade 3 TEAE and [redacted]/165 ([redacted]) patients experienced ≥1 Grade 4 TEAE. The most common Grade 3 or 4 TEAEs were:

- neutropenia (108/165 [65.5%] patients)
- anaemia (62/165 [37.6%] patients)
- lymphopenia (57/165 [34.5%] patients).

Clinical advice to the EAG is that CRS is manageable in NHS clinical practice but may require additional inpatient stays. Clinical advice to the EAG is that cytopenias are commonly associated with RRMM treatments and are well-managed in NHS clinical practice.

When considering all infection types collectively, [redacted]/165 ([redacted]) patients experienced ≥1 treatment-emergent infections; [redacted] ([redacted]) patients experienced a maximum ≥Grade 3 infection.[19] The company reported (CS, p112 and Figure 35) that patients who switched from Q1W to Q2W dosing experienced fewer new onset ≥Grade 3 infections than patients who remained on weekly dosing.

[redacted]/165 patients ([redacted]) experienced hypogammaglobulinemia and [redacted]/165 ([redacted]) patients subsequently received intravenous immunoglobulins (IVIg).[19] However, only [redacted]/165 ([redacted]) patients experienced ≥1 hypogammaglobulinaemia TEAE judged by the investigator as relating to teclistamab.[19]

3.7.2 Death

[redacted]/165 ([redacted]) patients experienced a Grade 5 TEAE (i.e., death). Cause of death was:

- an AE for [redacted]/165 ([redacted]) patients, including 18/165 (10.9%) patients who experienced maximum Grade 5 COVID-19
- progressive disease for [redacted]/165 ([redacted]) patients.

3.7.3 Adverse events of special interest

The adverse events of special interest (AESIs) for teclistamab are CRS and neurotoxicity (CS, p150). In the MajesTEC-1 trial:

- [redacted]/165 ([redacted]) patients experienced ≥1 any grade CRS event; nearly all events were Grade 1 or Grade 2, one patient experienced maximum Grade 3 CRS and [redacted] patients experienced maximum Grade 4 or 5 CRS (CS, Table 32)
- [redacted]/165 ([redacted]) patients experienced ≥1 any grade neurotoxicity TEAE; [redacted] events were Grade 1 or Grade 2, [redacted] patient experienced maximum Grade 4 neurotoxicity and [redacted] patients experienced maximum Grade 3 or 5 neurotoxicity[19]
- specifically, [redacted]/165 ([redacted]) patients experienced ≥1 any grade ICANS event; [redacted] events were maximum Grade 1 or Grade 2.[19]

3.7.4 Real-world evidence safety and tolerability results: teclistamab

Dima study[20] and Riedhammer study[21] safety results were largely consistent with the MajesTEC-1 trial safety results:

- in the Riedhammer study,[21] the most common AEs were CRS, anaemia and thrombopenia
- a slightly smaller proportion of patients experienced CRS in the Dima study[20] (68/106 [64%] patients) and in the Riedhammer study[21] (72/123 [58.5%] patients) than in the MajesTEC-1 trial ([redacted]/165 [[redacted]] patients); nearly all CRS events were Grade 1 or Grade 2

- a slightly larger proportion of patients experienced ICANS in the Dima study[20] (15/106 [14%] patients) and in the Riedhammer study[21] (9/123 [7.3%] patients) than in the MajesTEC-1 trial ([redacted]/165 [redacted] patients); most ICANS events were Grade 1 or Grade 2
- a smaller proportion of patients experienced ≥1 infection in the Dima study[20] (33/106 [31%] patients) and in the Riedhammer study[21] (67/123 [54.5%] patients) than in the MajesTEC-1 trial ([redacted]/165 [redacted] patients); approximately half of infection events were Grade ≥3
- a similar proportion of patients received IVIg in the Dima study[20] (44/106 [42%] patients) as in the MajesTEC-1 trial ([redacted]/165 [redacted] patients); the number of patients who received IVIg was not reported for the Riedhammer study.[21]

3.7.5 Safety and tolerability results: PomDex

Safety and tolerability data were not collected in the UK RW TCE RRMM study.[28] To compare the safety of teclistamab versus PomDex, the EAG reviewed PomDex safety data from the pomalidomide SmPC.[39] The EAG's naïve comparisons show that:

- similar to teclistamab, the most common AEs in PomDex studies were cytopenias including anaemia (45.7%) and neutropenia (45.3%); however, a [redacted] proportion of patients in the MajesTEC-1 trial experienced anaemia ([redacted]) and neutropenia ([redacted]) than in the PomDex studies
- fatigue (28.3%) was the third most common AE in PomDex studies; a [redacted] proportion of patients in the MajesTEC-1 trial experienced fatigue ([redacted]/165 [redacted] patients)
- similar to teclistamab, the most common Grade 3 or Grade 4 AEs in PomDex studies were cytopenias including neutropenia (41.7%), anaemia (27%) and thrombocytopenia (20.7%); however, a [redacted] proportion of patients in the MajesTEC-1 trial experienced Grade 3 or 4 neutropenia ([redacted]), anaemia ([redacted]) and thrombocytopenia ([redacted]) than in the PomDex studies
- infection (considered collectively) was the most common non-haematological AE in the PomDex studies (55.0%); a [redacted] proportion of patients ([redacted]) in the MajesTEC-1 trial experienced treatment-emergent infections[19] than in the PomDex studies.

Clinical advice to the EAG is that CRS and ICANS are not associated with PomDex treatment. Clinical advice to the EAG is that AEs are more common with teclistamab than other RRMM treatments but can be managed routinely in NHS clinical practice.

3.8 EAG's summary and conclusions of the clinical effectiveness section

The company provided clinical effectiveness evidence for teclistamab from one single arm trial (the MajesTEC-1 trial) and two RW retrospective studies (the Dima study[20] and the Riedhammer study[21]). The EAG considers that the MajesTEC-1 trial is a well-conducted trial that enrolled patients with TCE RRMM who had received ≥3 prior lines of treatment including an IMiD, a PI, and an anti-CD38 mAb.

Clinical advice to the EAG and the company is that PomDex is the main comparator to teclistamab for patients with TCE RRMM who have received ≥3 prior lines of treatment

including an IMiD, a PI and an anti-CD38 mAb and whose disease progressed on the last treatment received. Direct clinical effectiveness evidence was not available for the comparison of teclistamab versus PomDex and therefore the company conducted adjusted ITCs using IPD from the MajesTEC-1 trial and IPD from the UK RW TCE RRMM study, a retrospective registry study.

3.8.1 Direct clinical evidence: teclistamab

Clinical trial evidence

Clinical advice to the EAG and the company is that MajesTEC-1 trial patients are younger, fitter, more heavily pre-treated and less likely to have high risk cytogenetics than NHS patients with TCE RRMM; however, overall, the MajesTEC-1 trial results are generalisable to NHS patients.

Clinical advice to the EAG is that the MajesTEC-1 trial efficacy results show deep and sustained treatment responses (specifically, the outcomes, MRD negativity rate and sCR) for patients with TCE RRMM who are treated with teclistamab in the fourth-line setting. Overall, in the MajesTEC-1 trial, patient HRQoL improved. Clinical advice to the EAG is that there were no unexpected AEs and that the teclistamab safety profile is manageable.

Real-world evidence

Clinical advice to the EAG is that the Dima study[20] and the Riedhammer study[21] teclistamab populations were less fit and had a worse prognosis than the MajesTEC-1 trial All Treated Analysis Set population and therefore, in some respects, these patients may be more representative of NHS patients with TCE RRMM than MajestTEC-1 trial patients.

The Dima study[20] and the Riedhammer study[21] efficacy and safety results were consistent with the MajesTEC-1 trial results.

3.8.2 Indirect clinical evidence: teclistamab versus PomDex

Clinical advice to the EAG is that, overall, the UK RW TCE RRMM study PomDex cohort is more representative of NHS patients with TCE RRMM than the MajesTEC-1 trial, the Dima study[20] and the Riedhammer study[21] populations because the data are specific to the UK and the median number of prior lines of treatment is more similar to the number of treatments received by NHS patients.

The company carried out adjusted ITCs to compare the effectiveness (OS and TTNT, used as a proxy for PFS) of teclistamab versus PomDex using IPD from the MajesTEC-1 trial and the UK RW TCE RRMM study. The ITC results showed a statistically significant treatment effect

in favour of teclistamab over PomDex for both OS and TTNT. However, the EAG identified the following methodological flaws in the ITCs:

- the company was also unable to adjust for four priority prognostic factors identified by the company (cytogenetic profile, ISS stage, time to progress on last regimen, extramedullary plasmacytoma)
- the PH assumption was violated for both the OS and TTNT ITCs.

The EAG considers that the company ITCs are methodologically flawed and results may be unreliable.

3.8.3 Safety data

Clinical advice to the EAG is that the teclistamab safety profile is less favourable than the PomDex safety profile but that the AEs associated with teclistamab are manageable in NHS clinical practice.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of teclistamab as a treatment option for patients with TCE RRMM who have received ≥3 prior lines of treatment including an IMiD, a PI and an anti-CD38 mAb and whose disease progressed on the last treatment received. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook SLRs to identify and appraise i) published cost effectiveness evaluations ii) HRQoL data and iii) healthcare resource use (HCRU) and cost data for the population with TCE RRMM. The SLR target population was broader than the population defined in the decision problem as it included all patients with RRMM and did not restrict by TCE status or prior lines of treatment. The searches were not restricted by publication date; they were originally conducted in July 2020, with the latest update conducted in October 2023. The HCRU and cost data SLRs were conducted in parallel with the economic evaluation SLR.

Electronic database searches were designed to identify studies published from 2014 onwards. The company also searched conference proceedings, documents submitted to Health Technology Assessment (HTA) agencies and the bibliographies of all relevant SLRs and economic evaluations. Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (Appendix G, Appendix H and Appendix I).

The company's economic evaluation and HCRU/cost SLRs identified 169 unique studies that assessed interventions for patients with RRMM. Of these, 105 were published economic evaluations (including 49 HTA submission reports), and the remaining studies were cost per outcome analyses or budget impact models which were deemed less relevant for this appraisal. Of the included studies, eight reported data relating to patients with TCE RRMM (CS, Appendix G, Table 37). The company's HRQoL SLR identified 118 unique studies (CS, Appendix H, Table 44); of these, nine studies reported direct utility values for a TCE RRMM patient population (CS, Appendix H, Table 50).

4.2 EAG critique of the company's literature reviews

The EAG considers all the company's cost effectiveness evidence SLR methods were of a good standard (Table 16). The company's database searches were comprehensive and

search terms included a good combination of index terms and free text words relevant to the disease area. However, the EAG notes that two RW studies[20,21] of teclistamab were not identified by the company because they were published after the most recent search date (October 2023) and the UK RW TCE RRMM study was excluded in error during title and abstract screening.

Table 16 EAG appraisal of systematic review methods (cost effectiveness, HRQoL and healthcare resource use/cost)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Not reported
Was data extracted by two or more reviewers independently?	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were attempts to synthesise evidence appropriate?	Not applicable

EAG=External Assessment Group; HRQoL=health-related quality of life; LR*i*G=Liverpool Reviews and Implementation
Source: LR*i*G in-house checklist

4.2.1 EAG conclusion

The EAG considers the methods used to conduct the company's systematic reviews of cost effectiveness evidence, HRQoL and healthcare resource use studies were of a good standard.

4.3 EAG summary and critique of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 17 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	Yes
Comparators	As listed in the scope developed by NICE	The company considered PomDex was the only relevant comparator based on feedback from clinical experts and data from a UK RW TCE RRMM cohort study (CS, Table 1)
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	NA
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	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

CS=company submission; EAG=External Assessment Group; EQ-5D=EuroQol 5 dimensions; NA=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care; PomDex=pomalidomide plus low-dose dexamethasone; PSS=Personal Social Services; QALY=quality adjusted life year; RRMM=relapsed or refractory multiple myeloma; RW=real world; SLR=systematic literature review; TCE=triple-class exposed
Source: EAG assessment of NICE Reference Case[40]

Table 18 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	Limited long-term clinical effectiveness evidence available for teclistamab and PomDex
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partial	See EAG revisions R6 and R7, Section 6.9
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

EAG=External Assessment Group
Source: Drummond and Jefferson (1996)[41]

4.4 Model structure

The company developed a de novo partitioned survival model in Microsoft® Excel to evaluate the cost effectiveness of teclistamab for treating RRMM after at least three prior therapies. This model consists of three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. Patients enter the model in the PF health state and are at risk of moving to either the PD health state or the death health state. Patients who progress to the PD health state are only at risk of progressing to the death health state; the death health state is an absorbing health state. Estimates of the proportions of patients in each health state who are treated with teclistamab are generated by parametric distributions fitted to IPTW-adjusted MajesTEC-1 trial OS and TTNT (proxy for PFS) K-M data. For patients treated with PomDex, health state membership is determined by parametric distributions fitted to UK RW TCE RRMM cohort study OS and TTNT K-M data. Utility values and costs assigned to each health state are used to estimate total QALYs and total costs. An illustration of the company model structure is presented in Figure 1.

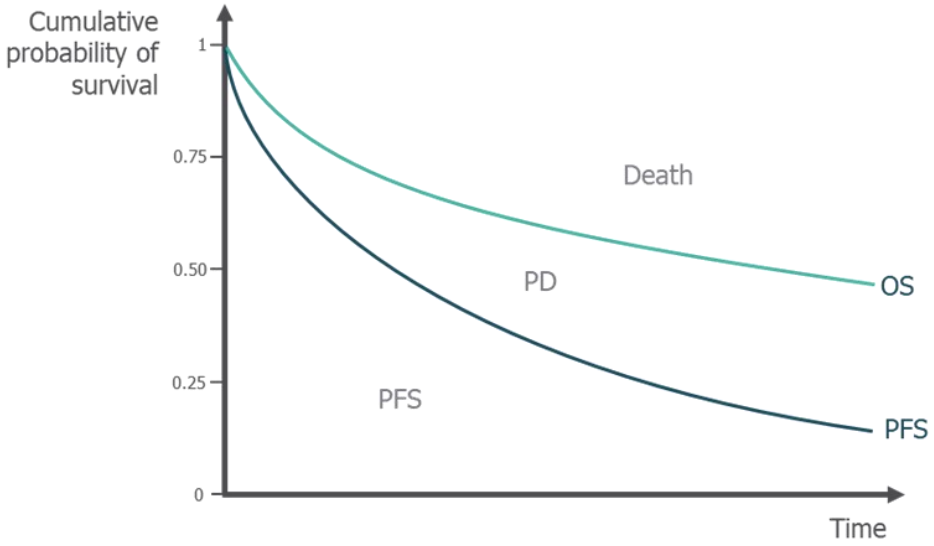

Figure 2 Structure of the company model

CS=company submission; OS=overall survival; PD=progressed disease; PFS=progression-free state
Source: CS, Section B.3.2.2, Figure 36.

4.5 Population

The company defined the population of interest as adult patients with RRMM who have received at least three prior therapies and have demonstrated disease progression on their last therapy, in accordance with the conditional MHRA marketing authorisation for teclistamab.[9] The baseline parameters used in the company model reflect UK RW TCE RRMM cohort study baseline patient characteristics (Table 19).

Table 19 Model population characteristics

Characteristics	TCE RRMM population	Source
Mean age, years	[redacted]	MajesTEC-1 trial data adjusted to align with the UK RW TCE RRMM cohort study population using IPTW with ATC weights
Proportion of female patients, %	[redacted]	
Mean body weight, kg	[redacted]	

ATC=average treatment effect for the control; CS=company submission; IPTW=inverse probability of treatment weighting; RRMM=relapsed or refractory multiple myeloma; TCE=triple-class exposed
Source: CS, Table 34

4.6 Interventions and comparators

The modelled intervention is teclistamab. Teclistamab is administered until disease progression or unacceptable toxicity; patients receive two step-up doses (day 1: 0.06mg/kg; day 3: 0.3 mg/kg), followed by a regimen of Q1W SC injections (1.5 mg/kg) (CS, Table 3). In line with MajesTEC-1 trial data, the company has assumed that patients switch from Q1W to Q2W administrations if they have a complete response or better for ≥6 months.

The comparator included in the cost effectiveness model is PomDex (CS, Table 2). PomDex modelled doses are as per the pomalidomide marketing authorisation[42] i.e., pomalidomide

(4mg) orally once daily for the first 21 days of a 28-day treatment cycle and dexamethasone (40mg) orally once daily on days 1, 8, 15 and 22 of the 28-day treatment cycle. Patients treated with PomDex are assumed to continue to receive treatment until disease progression or unacceptable toxicity.

4.7 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 1 week and a half-cycle correction was applied to health outcomes and costs to account for mid-cycle progressions. The model time horizon was 40 years and costs and outcomes were discounted at a rate of 3.5% per annum.

4.8 Treatment effectiveness and extrapolation

The MajesTEC-1 trial and the UK RW TCE RRMM cohort study have shorter follow-up periods (median follow-up of 30.4 and 26.0 months, respectively) than the model time horizon (40 years), and therefore available OS and PFS data were extrapolated.

4.8.1 Overall survival (OS)

Teclistamab

In accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[43] guidance, the company fitted six standard parametric distributions (exponential, generalised gamma, Gompertz, loglogistic, lognormal and Weibull) to IPTW-adjusted MajesTEC-1 trial OS K-M data. The choice of distribution used was determined by considering:

- the statistical goodness of fit assessed using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores
- visual inspection of the extrapolations against K-M curves
- clinical plausibility of extrapolations, based on long-term survival estimates at 5, 10 and 15 years elicited from clinical experts

The company selected the lognormal distribution to model OS; this distribution provided the best statistical and visual fit to the IPTW-adjusted MajesTEC-1 trial OS K-M data. However, compared to the survival estimates provided by company clinical experts, the lognormal distribution overestimated OS at 15 years. The company considered that not all MajesTEC-1 trial subsequent treatments are routinely available in UK clinical practice and this may have had an impact on long-term survival estimates. The company therefore further adjusted the MajesTEC-1 trial OS K-M data using the two stage method to reduce the survival time of patients who received subsequent treatments that are not available to NHS patients. Following this adjustment, long-term OS estimates decreased marginally but still remained above the

range suggested by company clinical experts (CS, Table 39). The company therefore calibrated the lognormal extrapolation by attenuating the mortality rate in each model cycle between 5 and 15 years so that survival estimates at 10 and 15 years corresponded to the midpoints of the range of survival estimates provided by clinical experts (10% and 3% respectively).

PomDex

The company assessed the proportionality of teclistamab (MajesTEC-1 trial) and PomDex (UK RW TCE RRMM cohort study) OS data and concluded that the PH assumption was violated (CS, Appendix N). The company therefore independently fitted parametric distributions to the UK RW TCE RRMM cohort study OS K-M data using the same approach used to fit distributions to MajesTEC-1 trial teclistamab OS data. The company selected the Gompertz distribution to model OS for patients treated with PomDex as it had the best statistical fit and generated long-term survival estimates that were within the range of OS estimates suggested by clinical experts.

All extrapolations used to generate OS estimates were capped by age- and sex-matched general population mortality rates sourced from the Office for National Statistics (ONS) national life tables.[44]

4.8.2 Progression-free survival (PFS)

In the company model, TTNT is used as a proxy for PFS as PFS data were not collected in the UK RW TCE RRMM cohort study; this approach was supported by the similarity of MajesTEC-1 trial PFS and TTNT data (see Section 3.3.4 and by clinical expert opinion.[45]

Teclistamab

The company fitted six standard parametric distributions to IPTW-adjusted MajesTEC-1 trial TTNT K-M data, and followed the same approach used to fit distributions to MajesTEC-1 trial teclistamab OS data (Section 4.8.1). The company selected the lognormal distribution to model PFS for patients treated with teclistamab as this distribution provided the best statistical and visual fit to the IPTW-adjusted MajesTEC-1 trial TTNT K-M data. However, as was the case when fitting a distribution to OS data, the proportions of patients who were progression-free and alive at 10 and 15 years were above the ranges of estimates at these time points provided by clinical experts. Using the same approach when modelling OS, the company calibrated the lognormal extrapolation by attenuating the PFS hazard in each model cycle between 5 and 15 years, so that PFS estimates at 10 and 15 years corresponded to the midpoints of the ranges of PFS estimates provided by clinical experts (5% and 1% respectively).

PomDex

The company assessed the proportionality of teclistamab (MajesTEC-1 trial) and PomDex (UK RW TCE cohort study) PFS data and concluded that the PH assumption was violated (CS, Appendix N). The company therefore independently fitted parametric distributions to the UK RW TCE RRMM study TTNT K-M data using the same approach used to fit distributions to MajesTEC-1 trial teclistamab OS data. The company selected the Gompertz distribution as this distribution had the best statistical fit and generated long-term survival estimates that were within the ranges suggested by clinical experts.

4.9 Health-related quality of life

4.9.1 Teclistamab utility values

HRQoL data were collected from MajesTEC-1 trial patients using the EQ-5D-5L questionnaire. EQ-5D-5L data were mapped to EQ-5D-3L (English value set) using the algorithm developed by the DSU[46] to generate utility values. PF health state time-dependent utility values were implemented in the company model for patients treated with teclistamab (Table 20); this approach was supported by MajesTEC-1 trial EQ-5D data and clinical expert opinion.[45] The company did not implement time dependent utilities for patients in the PD health state due to insufficient MajesTEC-1 trial data.

Table 20 Health state utility values for patients treated with teclistamab

Health state	Time (number of 28-day cycles)	Utility	SE	Source
Progression-free	0	[redacted]	[redacted]	MajesTEC-1 (August 2023 DCO, CS model with the lowest AIC)
	2	[redacted]	[redacted]	
	4	[redacted]	[redacted]	
	6	[redacted]	[redacted]	
	8	[redacted]	[redacted]	
	10	[redacted]	[redacted]	
	12	[redacted]	[redacted]	
	14	[redacted]	[redacted]	
	16	[redacted]	[redacted]	
	18	[redacted]	[redacted]	
	20	[redacted]	[redacted]	
	22	[redacted]	[redacted]	
	24 or more	[redacted]	[redacted]	
Progressed disease	All model cycles	[redacted]	[redacted]	

AIC=Akaike information criterion; CS=company submission; DCO=data cut off; SE=standard error
Source: CS, Table 52 and Table 53

4.9.2 PomDex utility values

The PF and PD health state time-independent utility values were **not** implemented in the company model for patients receiving PomDex; the values used by the company were those accepted by NICE ACs during the earlier appraisals of PomDex[15,47] (Table 21). The company considered that modelling time-dependent utility values would not be appropriate as the observed MajesTEC-1 trial variation in utility values was due to response to treatment and patients treated with PomDex were unlikely to ever achieve a CR and the associated improvement in HRQoL.

Table 21 Health state utility values for patients treated with PomDex in company base case

Health state	Utility	SE	Source
Progression-free	0.610	0.010	MM-003 trial[48] (TA510[47]/TA783[15])
Progressed disease	0.570	0.010	

CS=company submission; PomDex=pomalidomide plus low-dose dexamethasone; SE=standard error
Source: CS, Table 54

4.9.3 Adverse event disutility

Grade ≥3 TEAEs that occurred in at least 5% of patients treated with teclistamab (MajesTEC-1 trial) or PomDex (MM-003 trial[48]) are modelled. As CRS and neurotoxicity are AESIs associated with teclistamab, Grade 1-2 events were also modelled, regardless of incidence. The QALY loss associated with each AE was calculated by multiplying the incidence rate for each AE by an associated disutility and duration (Table 22). The total QALY loss for all AEs was then applied as a one-off decrement in the first model cycle.

Table 22 Adverse event disutilities applied in company model

Adverse event	Utility decrement	Decrement sources	Duration of AE (days)	Duration sources
Anaemia	-0.3100	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	MajesTEC-1 trial (August 2023 DCO)[19]
Asthenia and fatigue	-0.1150	Lloyd et al 2006[50]	[redacted]	
CRS, Grade 1–2	-0.1109	CARTITUDE-1[51]	[redacted]	
CRS, Grade 3+	[redacted]	Patients with Grade 3+ CRS are assumed to experience 0 quality of life	[redacted]	
Dyspnoea	-0.0500	Doyle et al 2008[52]	[redacted]	
Febrile neutropenia	-0.3900	TA510 (based on Launois et al)[47]	[redacted]	
Hypertension	0.0000	TA573 (assume to be controlled by medication and therefore have no impact on HRQoL)[53]	[redacted]	
Hypophosphatemia	-0.1500	TA559 (2018)[54]	[redacted]	
Leukopenia	-0.0650	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	
Lymphopenia	-0.0650	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	
Neurotoxicity, Grade 1-2	0.0000	Assumed to be captured as part of CRS disutility	[redacted]	
Neurotoxicity, Grade 3+	0.0000	Assumed to be captured as part of CRS disutility	[redacted]	
Neutropenia	-0.1450	Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	
Pneumonia	-0.1900	Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	
Thrombocytopenia	-0.3100	Brown 2013/Partial Review TA171 (Bacelar et al)[49]	[redacted]	

AE=adverse event; DCO=data cut off; CRS=cytokine release syndrome; PomDex=pomalidomide plus low-dose dexamethasone; QALY=quality adjusted life year; TA=technology appraisal
Source: CS, Table 51

4.10 Resource use and costs

4.10.1 Drug costs

Unit costs

The costs of teclistamab and PomDex are presented in Table 23. Teclistamab dosing is based on weight and the dose per administration was estimated using mean MajesTEC-1 trial patient weight ([redacted]kg). In the company base case, vial sharing was assumed but wastage was modelled in 15% of patients receiving teclistamab, based on the level of wastage modelled in the NICE appraisal for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies.[55]

Table 23 Drug costs used in the economic model for teclistamab and PomDex

Intervention	Pack Size	Strength	Price per pack	Source
Teclistamab*	1	30mg/3ml solution for injection	£775.14	BNF[56-58]
	1	153mg/1.7ml solution for injection	£3,952.78	BNF[56-58]
Pomalidomide	21	4mg capsules	£8,884.00	BNF[58,59]
Dexamethasone (oral)	50	2.0mg	£2.62	eMIT[58]

*PAS price used in company model
BNF=British National Formulary; CS=company submission; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme; PomDex=pomalidomide plus low-dose dexamethasone
Source: CS, Table 55

Dose interruptions and dose switching

During clarification, the company identified and corrected an error relating to the proportion of teclistamab maintenance doses missed. After adjusting the number of expected doses to account for time until to treatment discontinuation and patients who switched to unlicensed dosing schedules, [redacted] of teclistamab maintenance doses were assumed to be missed in the company model (company clarification response, Table A1). Dose skipping was applied from Cycle 2 onwards as no patients missed a step-up dose in the MajesTEC-1 trial. In absence of any dose adherence data, the company assumed that patients treated with PomDex did not skip any doses and instead applied a relative dose intensity of 96.41% (corresponding to the complement of the proportion of PomDex packs not distributed to patients in TA427[11]).

In the company model, a proportion of patients remained on treatment with teclistamab and those who had a CR or better for ≥6 months switched from Q1W to Q2W administrations. The proportion of patients switching was determined by fitting parametric distributions to MajesTEC-1 trial dose switching K-M data using the same approach used to fit distributions to MajesTEC-1 trial teclistamab OS data. Despite complete K-M data, the company preferred to fit parametric distributions to smooth out the stepwise K-M data caused by dose switching events. The company selected the Gompertz distribution to model teclistamab dose switching as this distribution provided the best statistical fit.

Time on treatment

The company estimated the proportion of patients remaining on teclistamab treatment by fitting parametric models to MajesTEC-1 trial time to treatment discontinuation (TTD) K-M data, using the same approach used to fit distributions to MajesTEC-1 trial teclistamab OS data. The Gamma distribution was selected in the base case to model the proportion of patients remaining on teclistamab treatment over time as the company considered that this distribution provided clinically plausible long-term survival estimates.

As TTD data were not collected as part of the UK RW TCE RRMM cohort study, the company estimated PomDex time on treatment by calculating the ratio of teclistamab PFS (using TTNT as a proxy) to teclistamab TTD data; this ratio was then applied to the PomDex PFS extrapolation.

Co-medication costs

In line with the teclistamab SmPC[60] and a recent PomDex appraisal (TA510[47]), the company included co-medication costs during the step-up dosing regimen for patients receiving teclistamab and patients receiving PomDex (Table 24). Pre-medication costs, including granulocyte colony stimulating factor (G-CSF), red blood cell (RBC) transfusions and platelet transfusions were also modelled for patients receiving PomDex. The proportions of patients receiving each medication are presented in Table 25.

Table 24 Co-medication, pre-medication and immunoglobin unit costs

Medication	Units	Strength	Price per pack or unit cost	Dosage per administration or number of doses received	Drug or monitoring cost per admin (£)	Source
Dexamethasone PO 2 mg	28	2.0mg	£3.13	16mg	0.89	BNF[61] 2024
Paracetamol (acetaminophen)	100	500mg	£0.60	825mg	0.01	BNF[57] 2024
Diphenhydramine	20	25mg	£3.87	50mg	0.39	MIMS,[62] (Nytol)
Acetylsalicylic acid	100	75mg	£0.46	150mg	0.01	eMIT[58] 2023
G-CSF	-	-	£59.75	1	-	TA510[47] costs inflated from 2014/15 to 2021/22 using the NHSCII P&P Index[63,64]
RBC transfusion	-	-	£138.15	3	-	
Platelet transfusion	-	-	£223.31	4.79	-	
Octagam (Ig)	1	10mg	£690.00	29.9g	-	BNF[65] 2024
Cuvitru (Ig)	1	10mg	£570.00	29.9g	-	BNF[66] 2024

BNF=British National Formulary; CS=company submission; eMIT=electronic market information tool; G-CSF=granulocyte-colony stimulating factor; Ig=immunoglobin; MIMS=monthly index of medical specialities; NHSCII P&P=National Health Service Cost Inflation Index Pay & Prices; RBC=red blood cell
Source: CS, Table 59, Table 60 and Table 64

Table 25 Proportion of patients receiving each co-medication

Medication	Usage among patients treated with teclistamab	Usage among patients treated with PomDex	Source
Dexamethasone PO 2mg	100%	0%	Teclistamab SmPC[5]; TA510[47] and TA783[15]
Paracetamol (acetaminophen)	100%	0%	
Diphenhydramine	100%	0%	
Acetylsalicylic acid	0%	33%	
G-CSF	0%	43%	
RBC transfusion	0%	49%	
Platelet transfusion	0%	20%	

CS=company submission; G-CSF=granulocyte-colony stimulating factor; PO=per os (by mouth); PomDex=pomalidomide plus low-dose dexamethasone; RBC=red blood cell; SmPC=Summary of Product Characteristics
Source: CS, Table 59 and Table 60

Hypogammaglobulinaemia has been reported in patients receiving teclistamab; the company modelled the cost of immunoglobulin (Ig) usage in patients receiving teclistamab using the observed frequency and duration of infusions in the MajesTEC-1 trial (Table 26).

Table 26 Immunoglobin dosing regimen for patients treated with teclistamab

Method of administration	Mean number of doses	Proportion of patients	Source
IV	[redacted]	[redacted]	MajesTEC-1 trial (August 2023 DCO)
SC	[redacted]	[redacted]	

CS=company submission; DCO=data cut-off; IV=intravenous; SC=subcutaneous
Source: CS, Table 62

Subsequent treatment costs

Following disease progression on initial treatment, the company assumed, based on data from a real world study of UK MM patients,[67] that 52.6% of patients would receive subsequent treatment. The company model included the cost of the subsequent treatments received by 2% of patients in either the MajesTEC-1 trial or the UK RW TCE RRMM cohort study. The proportion of patients receiving each subsequent treatment in both the MajesTEC-1 trial and UK RW TCE RRMM cohort study were re-weighted to remove the subsequent treatment regimens that are not routinely available in UK clinical practice (Table 27). This assumption was validated by UK clinical experts and, in line with the TA889[68] NICE AC's preferred assumption, patients in both arms of the model were assumed to receive subsequent treatments for a median of 4 months (sourced from Yong et al[69]).

Table 27 Modelled subsequent treatment distributions (re-weighted)

Treatment	Teclistamab (MajesTEC-1 trial)	Treatment	PomDex (UK RW TCE RRMM study)
Cyclophosphamide+ pomalidomide+ dexamethasone	[redacted]	Bortezomib+panobinostat+ dexamethasone	58.3%
Dexamethasone	[redacted]	Melphalan+thalidomide	10.9%
Melphalan+dexamethasone	[redacted]	Cyclophosphamide+ thalidomide	8.3%
Bortezomib+ cyclophosphamide+ dexamethasone	[redacted]	Melphalan	5.2%
Cyclophosphamide+ dexamethasone	[redacted]	Cyclophosphamide+ dexamethasone	4.7%
Bendamustine	[redacted]	Cyclophosphamide+ pomalidomide+ dexamethasone	4.7%
Bortezomib+dexamethasone	[redacted]	Bendamustine+thalidomide	3.1%
Bendamustine+prednisolone	[redacted]	Bortezomib+dexamethasone	2.6%
Cyclophosphamide + etoposide + prednisolone + vincristine	[redacted]	Bendamustine	2.1%
Pomalidomide+dexamethasone	[redacted]		

CS=company submission; RRMM=relapsed or refractory multiple myeloma; RW=real world; TCE=triple-class exposed
Source: CS, Table 68

4.10.2 Health state costs and resource use

Health state costs

The company applied health state specific monitoring costs to the healthcare resource use frequencies reported in TA427[11] (Table 28).

Table 28 Health state resource use costs used in the company model

Resource use	Unit cost	Frequency per week			Source
		PFS (on treatment)	PFS (off treatment)	PD	
Haematologist visit	£209.41	0.23	0.08	0.08	TA427[11]
Full blood count	£2.96	0.21	0.21	0.39	
Biochemistry	£7.73	0.19	0.19	0.33	
Average weekly cost		**£50.25**	**£18.84**	**£20.46**	Calculation

CS=company submission; PD=progressed disease; PFS=progression-free survival
Source: CS, Table 65

Administration costs

The company included administration costs for both initial and subsequent treatments; unit costs were sourced from the NHS Cost Collection[64] (Table 29). As PomDex is administered orally, a one-off administration cost was applied on treatment initiation. Teclistamab is administered subcutaneously, and a cost was applied for each dose administration. In

addition, the teclistamab SmPC[5] states that during the step-up dosing regimen patients should remain within the proximity of a healthcare facility and monitored for 48 hours after administration of all step-up doses. The company therefore assumed patients treated with teclistamab would spend 4 days in hospital during the first weekly cycle and 2 days in hospital during the second weekly cycle. Hospitalisation costs (inpatient stay per day=£695.72[64]) were included as part of the teclistamab drug administration cost for teclistamab.

Table 29 Drug administration costs included in the company model

Administration	Cost	Source
Complex first IV infusion	£485.23	NHS Cost Collection 2021–22, SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – Daycase and Regular Day/Night admissions + blood sample prior 1st infusion[64]
Other IV administration	£326.46	NHS Cost Collection 2021–22, SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle – Outpatient[64]
Each SC administration	£119.00	NHS Cost Collection 2021–22, N10AF: Specialist Nursing, Cancer Related, Adult, Face to face[64]
Oral drug initiation	£197.25	NHS Cost Collection 2021–22, SB11Z: Deliver Exclusively Oral Chemotherapy – Outpatient[64]
Oral drug subsequent	£0.00	Assumption

CS=company submission; IV=intravenous; NHS=National Health Service; SC=subcutaneous
Source: CS, Table 57

4.10.3 Adverse events costs

The AEs included in the company model are presented in Table 22. The company included the cost of managing AEs experienced by patients receiving treatment; unit costs for each AE were sourced from the NHS Cost Collection[64] (Table 30). AE costs were applied as a one-off cost in the first model cycle.

Table 30 Adverse event unit costs applied in the company model

AE	Unit cost	Source
Anaemia	£1,603.06	NHS Cost Collection 2021–22, SA09: Weighted Average of Non-Elective Admissions[64]
Asthenia and fatigue	£1,512.86	NHS Cost Collection 2021-22, WH17: Weighted Average of Non-Elective Admissions[64]
CRS, Grade 1–2	£1,531.46	Assumed to be the cost of tocilizumab, 8mg/kg for 2 doses based on feedback received from UK clinical experts on the management of Grade 1–2 CRS AEs in clinical practice.[70] BNF 2024
CRS, Grade 3+	£7,962.02	Assumed to be the cost of tocilizumab, 8mg/kg for 2 doses, plus 3 days ICU based on feedback received from UK clinical experts on the management of Grade 3+ CRS AEs in clinical practice.[70]
Dyspnoea	£539.17	NHS Cost Collection 2021-22, DZ19L, DZ19M, DZ19N: Weighted average of Day Case[64]
Febrile neutropenia	£2,335.50	NHS Cost Collection 2021–22, SA35: Weighted Average of Non-Elective Admissions[64]
Hypertension	£781.13	NHS Cost Collection 2021-22, EB04Z: Weighted Average of Non-Elective Admissions[64]
Hypophosphatemia	£1,831.57	Assumed equal to hypokalaemia, as per TA658[14]
Leukopenia	£1,772.97	NHS Cost Collection 2021/22, SA08: Weighted Average of Non-Elective Admissions[64]
Lymphopenia	£1,772.97	NHS Cost Collection 2021/22, SA08: Weighted Average of Non-Elective Admissions[64]
Neurotoxicity, Grade 1–2	£0.00	Assumed to be captured within the hospitalisation cost of CRS (Grade 1–2)
Neurotoxicity, Grade 3+	£0.00	Assumed to be captured within the hospitalisation cost of CRS (Grade 3+)
Neutropenia	£2,335.50	NHS Cost Collection 2021-22, SA35: Weighted Average of Non-Elective Admissions[64]
Pneumonia	£1,273.81	NHS Cost Collection 2021-22, CB02: Weighted Average of Non-Elective Admissions[64]
Thrombocytopenia	£2,163.16	NHS Cost Collection 2021-22, SA12: Weighted Average of Non-Elective Admissions[64]

BNF=British National Formulary; CRS=cytokine release syndrome; CS=company submission; ICU=intensive care unit; NHS=National Health Service
Source: CS, Table 66

4.10.4 End-of-life costs

The company applied a one-off cost of terminal care to the proportion of patients who died in each model cycle. The end-of-life cost was £13,113.00. This cost was sourced from Personal Social Services Research Unit (PSSRU) oncology reference costs[63] and accounts for both hospital and social care costs (£11,407.00 and £1,706.00 respectively); this approach is in line with the approach taken in TA897.[71]

4.11 Severity modifier

The company calculated the absolute and proportional QALY shortfalls for patients with TCE RRMM who had received at least three prior therapies of PomDex (Table 31). Expected general population QALY values, using the age and gender values of patients in the UK RW TCE RRMM cohort study, were calculated using the severity modifier tool[72] developed by the Sheffield Centre for Health and Related Research (SCHARR). The company considered that teclistamab is eligible for a 1.2x severity modifier.

Table 31 Company QALY shortfall analysis results

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall		Severity modifier
		Absolute	Proportional	
[redacted]	[redacted]	[redacted]	[redacted]	1.2

CS=company submission; QALY=quality adjusted life year.
Source: CS, Table 70

5 COST EFFECTIVENESS RESULTS

The cost effectiveness results presented in this section were generated by the company's clarification model. The EAG has presented updated base case results but has not updated company sensitivity and scenario results.

The company base case pairwise deterministic results are presented in Table 32. Company base case pairwise probabilistic results (200 model iterations) are presented in Table 33. Both sets of results were generated using the PAS price for teclistamab and list prices for all other drugs.

Table 32 Company base case deterministic pairwise results (PAS price for teclistamab)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with x 1.2 severity modifier
Teclistamab	[redacted]	[redacted]	-	-	-	-
PomDex	£109,342	0.75	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Company clarification response Table B1

Table 33 Company base case probabilistic pairwise results (PAS price for teclistamab)

Treatment	Total costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with x 1.2 severity modifier
Teclistamab	[redacted]	[redacted]	-	-	-	-
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Company clarification model

5.1 Sensitivity analyses

The company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on 95% CIs or ±10% of the mean base case value. Parameters with no associated uncertainty (e.g., drug costs) or interdependent variables that cannot be varied individually (e.g., efficacy extrapolation parameters) were excluded. Cost effectiveness results were most sensitive to the mean body weight of patients, the final time-dependent utility value for the PF state and the PD health state utility value (CS, Figure 57).

5.2 Scenario analyses

The company conducted scenario analyses exploring alternative model assumptions based on clinical expert feedback and key drivers of model outputs. Cost effectiveness results were most sensitive to the scenarios that explored alternative health state utility values and the adjustment factor applied to the OS extrapolation for teclistamab (CS, Table 81).

5.3 Validation

The model structure, data sources and statistical analysis designs were reviewed by health economic and UK clinical experts in MM, including the selection of base case extrapolations used in the economic analysis. Verification and quality control checks of data inputs and programming code were performed by independent health economists. These procedures included verification of all input data with original sources and programming validation.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of teclistamab versus PomDex for patients with TCE RRMM.

6.1 Overview of modelling issues identified by the EAG

The EAG considers that the model algorithms that were implemented using heavily nested IF functions were problematic to check. Further, inefficient probabilistic sensitivity analysis (PSA) coding meant that each PSA run (10,000 iterations) took over 3 hours to complete. However, the EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the CS.

A summary of the EAG's critique is presented in Table 34.

Table 34 Summary of the EAG critique of the company's cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company model structure and time horizon are appropriate	NA
Population and comparators	• Use of weighted MajesTEC-1 trial teclistamab data compared to the UK RW TCE RRMM study PomDex cohort data is unlikely to produce precise estimates of the OS and PFS differences between the two treatments. However, clinical advice to the EAG is that this is unlikely to change the conclusion that teclistamab improves PFS and OS versus PomDex	NA
Overall survival	• The EAG is satisfied that the company approach to modelling OS for patients treated with teclistamab makes the best use of available evidence • The company approach to modelling OS for PomDex is inconsistent with the company approach to modelling OS for teclistamab **EAG revision**: attenuate OS for PomDex (mid-point of company clinical expert values)	6.2
Progression-free survival	• The company approach to modelling PFS for PomDex is inconsistent with the company approach to modelling PFS for teclistamab **EAG revision**: attenuate PFS for PomDex (mid-point of company clinical expert values)	6.3
Time to treatment discontinuation	• For consistency with the approach used by the company to generate PFS and OS estimates for teclistamab, the best-fitting teclistamab TTD distribution should have been used and teclistamab and PomDex should also have been informed by clinical expert opinion **EAG revision**: use lognormal distribution to generate teclistamab TTD estimates and then attenuate teclistamab and PomDex curves (mid-point of company clinical expert values)	6.4
Drug costs	• The company approach to teclistamab switching from Q1W to Q2W does not reflect the rules for switching regimen in the teclistamab SmPC[7] • The EAG is satisfied with the company approach to inclusion of RDI and treatment wastage **EAG revision**: patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportion switching at each time point is determined by MajesTEC-1 trial data	6.5

Aspect considered	EAG comment	Section of EAG report
Utility values	• Different utility values have been used for teclistamab and PomDex. Clinical advice to the company was that the same (MajesTEC-1 trial) utility values should have been used for both treatments **EAG revision**: use the same PF and PD health state utility values (derived from MajesTEC-1 trial data) for patients treated with teclistamab and PomDex	6.6
Proportion of patients receiving subsequent treatment	• The company has estimated the proportion of patients treated with teclistamab receiving subsequent treatment based on real world evidence. The EAG considers it is more appropriate to use MajesTEC-1 trial data **EAG revision**: the proportion of patients treated with teclistamab who receive subsequent treatment matches the proportion of patients who received subsequent treatment in the MajesTEC-1 trial	6.7
Modelled subsequent treatments	• The subsequent treatments received should be the same for patients treated with PomDex or teclistamab, with an adjustment for patients receiving teclistamab to reflect that they may receive PomDex as a subsequent treatment **EAG revision**: the UK RW TCE RRMM PomDex cohort subsequent treatment distribution is applied to patients treated with teclistamab and PomDex, with an adjustment to allow patients treated with teclistamab to receive PomDex as a subsequent treatment (MajesTEC-1 trial proportion)	6.7
Healthcare resource use	• The company has correctly applied costs and resource use for both treatment arms • In the model, the company has assumed the same Ig teclistamab use as in the MajesTEC-1 trial. The EAG considers this was appropriate as the trial outcomes reflect the use of Ig in the trial. The EAG considers the scenario using less Ig, in line with UK guidelines, is uninformative as it only leads to a reduction in costs (no change to efficacy)	NA
Adverse events	• The inclusion of AE disutilities may result in double counting given that the utility values are drawn from the MajesTEC-1 trial **EAG revision**: AE disutility values are not applied	NA
Half-cycle correction	• The company model cycle length was 1 week 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 only 1 week. No change made to the company model	NA
Company severity modifier	• A 1.2 modifier is appropriate to apply, even after EAG amendments are made to the company base case	6.8
PSA	• The company PSA included variation of unit costs which is inappropriate. EAG PSA runs have excluded unit costs from the PSA analysis	NA

AE=adverse event; EAG=External Assessment Group; Ig=immunoglobulin; NA=not applicable; OS=overall survival; PF=progression-free; PSA=probabilistic sensitivity analysis; Q1W=once weekly; Q2W=once every two weeks; QALY=quality adjusted life year; RDI=relative dose intensity; SmPC=Summary of Product Characteristics; TTD=time to treatment discontinuation; UK RW TCE RRMM=UK real world triple-class exposed relapsed or refractory multiple myeloma

6.2 Use of weighted MajesTEC-1 trial data to estimate OS and PFS for patients treated with teclistamab

The company teclistamab and PomDex OS and PFS estimates are based on weighted MajesTEC-1 trial OS and PFS K-M data and UK RW TCE RRMM study PomDex cohort IPD, respectively. MajesTEC-1 trial data were weighted using the methods described in Section 3.5.3. The company was unable to adjust for four priority prognostic factors (cytogenetic profile, ISS stage, time to progress on last regimen, extramedullary plasmacytoma). The EAG therefore has concerns that the teclistamab data and PomDex datasets were not well matched

in terms of patient baseline characteristics. Although clinical advice to the company and EAG is that it is likely that OS and PFS experienced by patients treated with teclistamab will be longer than OS and PFS experienced by patients treated with PomDex, the difference in long-term clinical effectiveness is uncertain.

6.3 Overall survival and progression-free survival

6.3.1 *Teclistamab OS and PFS distribution selection*

In line with DSU guidelines,[43] the company selected the parametric distributions used to generate OS and PFS estimates by fitting standard parametric distributions to MajesTEC-1 trial K-M data, choosing the best fitting distributions based on AIC and BIC scores and then using clinical advice to validate distribution choices.

The company stated that distributions more than two points higher than the distribution with the lowest AIC score provided a "a statistically significantly worse fit to the observed data" (CS p132). This statement is inaccurate as there is no method to test the statistical significance of distribution fit to K-M data based on differences in AIC scores.

Although the distributions chosen by the company were a good fit to MajesTEC-1 trial K-M data, the distributions did not generate 10- and 15-year estimates that aligned with clinical expert 10- and 15-year OS and PFS estimates. The company therefore attenuated ('fixed') the chosen distributions so that survival estimates aligned with the middle of the range of long-term OS and PFS *most likely values* provided by clinical experts. This approach resulted in clinically implausible 'kinks' in the company OS and PFS curves. Removing these kinks would require the application of 'smoothing' assumptions and would add additional layers of uncertainty to the model, namely how, and at what time point, smoothing should be implemented. The EAG considers that applying smoothing is unlikely to substantially change, or provide a more accurate estimate of, total QALYs associated with treatment with teclistamab.

The attenuation of OS and PFS distributions to ensure that long-term estimates aligned with clinician's long-term most likely estimates removed most of the differences in total QALYs generated by different distributions. For example, without attenuation, the difference in total QALYs between the OS distribution that generates the highest (Gompertz) number of QALYs and the distribution that generates the lowest (exponential) number of QALYs is [redacted] QALYs; with attenuation, this difference reduces to [redacted] QALYs. The EAG highlights that use of attenuation means that QALYs generated between Year 5 and Year 40 are based on clinician survival estimates rather than on MajesTEC-1 trial data.

Given the available data, the EAG is not able to offer any alternative approaches to generating teclistamab survival estimates that would produce more (or equally) clinically plausible OS and PFS estimates.

6.3.2 PomDex OS and PFS distribution selection

The company followed DSU guidelines[43] when fitting distributions to UK RW TCE RRMM study PomDex cohort OS and TTNT (used as a proxy for PFS) K-M data and used the fitted distributions to generate long-term survival estimates.

The EAG considers that the company's distribution choices were appropriate. However, although clinicians provided the company with likely OS and PFS estimates at 5, 10 and 15 years, in contrast with the company approach to generating survival estimates for patients treated with teclistamab, the company did not attenuate the PomDex OS and PFS curves so that survival estimates lay in the middle of clinician 10 and 15 year estimates. In response to clarification question B2, the company provided OS and PFS curves that generated estimates that reflected the mid-point of clinician 10 and 15 year likely values, as well as results from scenarios in which curve estimates aligned with the upper bound and lower bound of clinician 10 and 15 year likely values; the EAG has revised the model using this approach.

6.4 Time to treatment discontinuation

Teclistamab

The company followed DSU guidelines[43] when fitting a distribution to MajesTEC-1 trial TTD K-M data. Based on AIC scores, the distribution that was the best fit to MajesTEC-1 trial TTD K-M data was the lognormal distribution; however, this distribution generated TTD estimates that exceeded clinician likely 10 and 15 year values. The company therefore chose a distribution (Gamma) which was a poorer fit to MajesTEC-1 trial TTD K-M data but generated TTD estimates at 10 and 15 years that were close to clinician likely estimates.

The EAG considers that the company approach to curve selection for OS, PFS and TTD should have been consistent, i.e., the company should have selected the distribution that, based on AIC score, was the best fit to MajesTEC-1 trial TTD K-M data and then attenuated this distribution so that it generated estimates that aligned with clinician 10 and 15 year estimates. The EAG revised the company model by selecting the lognormal distribution (as it had the lowest AIC score) and then attenuated this distribution so that estimates aligned with the mid-point of clinician 10 and 15 year likely values, and ran scenario analyses using the upper and lower bound clinical expert estimates.

PomDex

The company generated TTD estimates for patients treated with PomDex by applying the teclistamab median TTD: teclistamab median PFS ratio to PomDex TTNT (a proxy for PFS) K-M data. Given the absence of PomDex TTD data, the EAG considers that this approach was appropriate. The EAG revised the company model by attenuating the PomDex TTD curve so that estimates matched clinician 10 and 15 year likely values.

6.5 Dose switching

Based on MajesTEC-1 trial regimen switching data, the company assumed that patients treated with teclistamab switch from a Q1W regimen to a Q2W regimen at the same rate as in the MajesTEC-1 trial. This resulted in model patients switching to the Q2W regimen from [redacted] weeks; however, in the teclistamab SmPC,[7] it is stated that a Q2W regimen is only permitted for patients who have experienced 6 months of ≥CR; the MajesTEC-1 trial mean time to CR was [redacted] months.

The MajesTEC-1 trial data show that, at 52 weeks, only [redacted] of patients still receiving teclistamab had switched to the Q2W regimen. The EAG revised the company model so that switching to the Q2W regimen started at 12 months and, from that point onwards, treatment switching reflected the proportion of MajesTEC-1 trial patients who switched to Q2W at different time points, i.e., [redacted] switched to the Q2W regimen between Week 0 and Week 52, and at Week 52, [redacted] of patients still receiving teclistamab switched to Q2W and, from Week 53 onwards, this proportion increases in line with MajesTEC-1 trial data.

6.6 Utility values

Progression-free survival health state utility values

The company has assumed that, in the PFS health state, the baseline utility value for patients treated with PomDex is lower than the baseline utility value for patients treated with teclistamab. The company has not presented any clinical evidence to support using differential utility values at baseline (i.e., before treatment with teclistamab or PomDex commenced).

In the company model, the utility values for patients treated with teclistamab increase substantially over the time spent in the PFS health state; however, utility values for patients treated with PomDex do not increase from baseline. Clinical advice to the company was that it was appropriate to model improving HRQoL over time for patients in the PFS health state, regardless of treatment.

In the absence of UK RW TCE RRMM study PomDex cohort time dependent PFS health state utility values, company clinical experts considered that it would be appropriate to use utility values (including time dependent [PFS] utility values) derived from MajesTEC-1 trial data (UK

Clinical Expert Validation Report,[73] p7) to reflect HRQoL for patients treated with PomDex. The EAG has followed clinical advice to the company and revised the company model by using utility values generated from MajesTEC-1 trial data to reflect HRQoL for patients treated with teclistamab and patients treated with PomDex.

Double counting

As the MajesTEC-1 trial HRQoL dataset includes data from patients who experienced AEs, the company adjustment to utility values to reflect the disutility associated with AEs is double counting. The EAG has revised the company model by removing this one-off disutility value.

Progressed disease health state utility value

In the company model, patients treated with teclistamab experience an instantaneous drop in utility on disease progression. For example, patients who have remained in the PF health state for 2 years, experience a drop in utility from [redacted] to [redacted]. This appears unlikely, especially if progression has been detected by investigative tests rather than because of symptom changes. Following the EAG revision (use of same [MajesTEC-1 trial] health state utility values), this instantaneous drop is also experienced by patients treated with PomDex. As patients treated with teclistamab spend longer in the PD health state than patients treated with PomDex, the instantaneous drop in utility on progression will have a greater impact on QALYs gained for patients treated with teclistamab than on QALYs gained for patients treated with PomDex.

6.7 Subsequent treatment

Proportion of patients receiving subsequent treatment

The company has assumed, based on real world study data[74] that the proportion of patients receiving subsequent treatment (52.6%) does not vary by prior treatment. As the modelled time patients treated with teclistamab spend in the PD health state is approximately twice that of the modelled time that patients treated with PomDex spend in the PD health state, patients treated with teclistamab should have a greater opportunity to receive subsequent treatment than patients treated with PomDex. The EAG therefore considers that, for patients treated with teclistamab, it is more appropriate to cost treatment based on the proportion of MajesTEC-1 trial patients who received subsequent treatment ([redacted]) rather than on real world study data.

Clinical advice to the EAG is that, for patients in the PD health state, choice of subsequent treatment is unlikely to affect clinical outcomes. Therefore, the choice of subsequent treatment should, as far as possible, closely align with the subsequent treatments prescribed to NHS patients, i.e., the subsequent treatments received by patients enrolled in the UK RW TCE RRMM study PomDex cohort. In the company model, subsequent treatments received by

patients treated with teclistamab are in line with MajesTEC-1 trial subsequent treatments, with the omission of treatments that are not routinely available to NHS patients and subsequent re-weighting of remaining treatments. The subsequent treatments received by patients treated with PomDex are in line with UK RW TCE RRMM study PomDex cohort subsequent treatments, with the omission of treatments that are not routinely available to NHS patients and subsequent re-weighting of remaining treatments.

The EAG has revised the company model so that the distribution of subsequent treatments received by patients is the same, irrespective of whether the patient was initially treated with teclistamab or PomDex, with the exception that some patients initially treated with teclistamab receive PomDex as a subsequent treatment. In the MajesTEC-1 trial, [redacted] of patients treated with teclistamab received PomDex as a subsequent treatment (CS, Table 71).

6.8 Severity modifier

The EAG agrees with the company that a severity modifier of 1.2 is appropriate.

6.9 Impact of EAG revisions on company base case cost effectiveness results

The EAG has made the following revisions to the company base case:

- OS and PFS for patients treated with PomDex attenuated to meet the mid-point of the company clinical expert likely values at 10 and 15 years (R1)
- TTD for patients treated with teclistamab and PomDex attenuated to meet the mid-point of the company clinical expert likely values at 10 and 15years (R2)
- patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportions who switch at each time point are determined by MajesTEC-1 trial data (R3)
- use the same PF and PD health state utility values (derived from MajesTEC-1 trial data) for patients treated with teclistamab and PomDex (R4)
- remove AE disutilities (R5)
- the proportion of patients treated with teclistamab who receive subsequent treatment matches the proportion of patients who received subsequent treatment in the MajesTEC-1 trial (R6)
- the UK RW TCE RRMM subsequent treatment distribution is applied to patients treated with teclistamab and PomDex, with an adjustment to allow patients treated with teclistamab to receive PomDex as a subsequent treatment (MajesTEC-1 trial proportion) (R7)

The EAG agrees with the company that the uncertainty around the validity of long-term estimates means that results from scenario analyses using lower and upper bound clinician likely OS and PFS estimates are informative. The EAG also considers that it is useful to explore the effect on cost effectiveness results of the following scenarios:

- OS and PFS for patients treated with teclistamab or PomDex attenuated to meet the lower (S1) and upper likely values (S2)
- TTD for patients treated with teclistamab and PomDex attenuated to meet the lower (S3) and upper likely values (S4)
- S5 (teclistamab optimistic scenario after implementation of R3-R7):
    - teclistamab: long term OS and PFS attenuated to the higher bound of likely company clinical expert and TTD to the lower likely value
    - PomDex: long term OS and PFS attenuated to the lower clinician likely values and TTD to the higher value
- S6 (teclistamab pessimistic scenario after implementation of R3-R7):
    - teclistamab: long term OS and PFS attenuated to the lower bound of likely clinical expert values and TTD to the higher likely value or to PFS if PFS is lower than TTD
    - PomDex: long term OS and PFS attenuated to the higher clinician likely values and TTD to the lower value.

Details of how the EAG revised the company model are presented in Appendix 3, Section 8.3 of this EAG report. Deterministic cost effectiveness results are provided in Table 36. Probabilistic cost effectiveness results for the EAG preferred base case and key scenarios are presented in Table 37. All results have been generated using list prices for all drugs except for teclistamab (PAS price).

All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 35.

Table 35 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
To be completed once the price tracker has been made available to the EAG	

CMU=Commercial Medicines Unit; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme

Table 36 Deterministic results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions to company base case	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Teclistamab dominates**	[redacted]	
R1) Attenuate PomDex OS and PFS (mid-point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R2) Use lognormal for teclistamab TTD and attenuate TTD for teclistamab and PomDex (mid-point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R3) Patients treated with teclistamab switch from a Q1W to a Q2W regimen at 12 months; no patients switch earlier than 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R4) PomDex utility values equal teclistamab utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R5) Remove AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R6) MajesTEC-1 trial proportion of patients treated with teclistamab receiving subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
R7) UK RW TCE RRMM PomDex cohort study proportion of patients receiving subsequent treatment (both model arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
B. EAG preferred base case (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Teclistamab dominates**	[redacted]	[redacted]
EAG scenarios									
S1) Attenuate teclistamab and PomDex OS and PFS using clinician lower likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
S2) Attenuate teclistamab and PomDex OS and PFS using clinician higher likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
S3) Attenuate TTD using clinician lower likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
S4) Attenuate TTD using clinician higher likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
S5) Teclistamab optimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Teclistamab dominates	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; Q1W=every week; Q2W=every 2 weeks; QALY=quality adjusted life year; RW TCE RRMM=real-world triple-class exposed relapsed or refractory multiple myeloma; TTD=time to treatment discontinuation

Table 37 Probabilistic results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions†	Teclistamab		PomDex		Incremental		ICER	NMB*	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 multiplier)	£/QALY		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A1. Company clarification base case with PSA corrected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred base case (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
† The EAG PSA runs exclude variation of unit costs
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PomDex=pomalidomide plus low-dose dexamethasone PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

6.10 Cost effectiveness conclusions

The company weighted MajesTEC-1 trial teclistamab data so that baseline characteristics matched UK RW TCE RRM study PomDex cohort patients. The EAG considers that the weighting approach used by the company was flawed.

Clinical advice to the company and EAG is that treatment with teclistamab is likely to be more clinically effective than treatment with PomDex, however, there appears to be considerable uncertainty within the clinical community around long-term survival for patients with TCE RRMM. In the absence of long-term clinical effectiveness data, company survival curves rely heavily on clinical expert estimates and cost effectiveness results are sensitive to survival projections; moreover, the company approach to incorporating clinical expert estimates into long-term OS, PFS and TTD is inconsistent.

The company used treatment dependent utility values. The EAG considers that, in line with expert clinical advice to the company, utility values derived from MajesTEC-1 trial data should have been used to represent the HRQoL of patients treated with teclistamab and patients treated with PomDex.

The EAG considers that, given the uncertainty around the comparative efficacy of teclistamab and PomDex and the reliance on clinical expert opinion to estimate long-term outcomes, the EAG pessimistic scenario cost effectiveness results may be the most informative; however, the cost effectiveness results presented by the company and by the EAG should be viewed as indicative rather than robust.

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8 APPENDICES

8.1 Appendix 1 Current service provision for NHS patients with MM

In NG35,[10] first-line treatment for patients with a new diagnosis of MM is dependent on whether ASCT is suitable for the patient. For patients for whom ASCT is suitable, induction treatment with bortezomib with dexamethasone with or without thalidomide is recommended as the first-line treatment option in NG35.[10] However, in February 2022, NICE recommended daratumumab plus bortezomib, thalidomide and dexamethasone as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable (TA763).[75] In March 2021, NICE recommended lenalidomide as maintenance treatment after ASCT or after ASCT consolidation treatment (TA680)[76].

In NG35,[10] thalidomide in combination with an alkylating agent and a corticosteroid is the preferred first-line treatment option for patients for whom ASCT is not suitable or appropriate. For patients who are unable to tolerate or have contraindications to thalidomide, bortezomib in combination with an alkylating agent and a corticosteroid is recommended.

Clinical advice to the EAG is that approximately 50% of NHS patients are eligible for ASCT and that approximately 90% of patients who are eligible for ASCT subsequently receive an ASCT. Clinical advice to the EAG is that in current NHS clinical practice, patients typically only receive one ASCT.

The following treatments are recommended as second-line treatment options regardless of transplantation eligibility in the first-line setting:

- lenalidomide with dexamethasone (TA586)[77]
- carfilzomib with dexamethasone (TA657)[78]
- carfilzomib with dexamethasone and lenalidomide (TA695)[79]
- bortezomib monotherapy (TA129)[80]
- daratumumab plus bortezomib and dexamethasone (TA573)[53]

The following treatments are recommended as third-line treatment options dependent on previous line of treatment but regardless of transplantation eligibility in the first-line setting:

- lenalidomide with dexamethasone (TA171)[16]
- panobinostat plus bortezomib and dexamethasone (TA380)[12]
- ixazomib plus lenalidomide and dexamethasone (TA505)[13]

8.2 Appendix 2 UK RW TCE RRMM study quality assessment using the ROBINS-I tool

Table 38 UK RW TCE RRMM study quality assessment using the ROBINS-I tool

Signalling questions[a]	Description	Company assessment	EAG assessment for median TTNT[b]	EAG assessment for median OS[b]
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 **If Y/PY to 1.1:** determine whether there is a need to assess time-varying confounding:	There is potential for the prognostic factors listed in Table 3 to have confounded intervention effects. However, it should be noted that feedback from clinical experts indicate that not all factors are considered to have a strong prognostic impact in the triple-class exposed treatment setting, potentially minimising the confounding effect of these variables.	Y	Y	Y
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 current LOT until death, embarkation (relocation outside of England) or until data cut-off. Follow up time was not split according to intervention received	N	Y Patients who progressed on their current LOT could have subsequently received an alternative intervention	Y Patients who progressed on their current LOT could have subsequently received an alternative intervention
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)	N/A	-	PY Clinical advice to the EAG is that patients with poor prognosis are less likely to respond to treatment and therefore may be more likely to discontinue or switch treatment	PY Clinical advice to the EAG is that patients with poor prognosis are less likely to respond to treatment and therefore may be more likely to discontinue or switch treatment
Questions relating to baseline confounding only				
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No analysis method to assess the influence of controlling for potentially confounding variables was performed	N	N	N

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?	N/A	-		
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No post-intervention variables were controlled for	**N**	**N**	**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?	No analysis to control for time-varying confounding was conducted	**N**	**N**	**N**
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?	N/A	-		
Risk of bias judgement	Confounding domains were generally reliably measured, but were not controlled for	**Serious**	**Serious**	**Serious**
Optional: What is the predicted direction of bias due to confounding?	N/A – no formal hypothesis tested for	-		
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	Participants were selected based on a pre-specified selection criterion, which did not include characteristics observed after treatment initiation	**N**	**N**	**N**
2.2. **If Y/PY to 2.1:** Were the post-intervention variables that influenced selection likely to be associated with intervention?	N/A	-		
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?	N/A	-		
2.4. Do start of follow-up and start of intervention coincide for most participants?	Patients were followed up from the start of their relevant line of therapy	**Y**	**Y**	**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?	N/A	-		
Risk of bias judgement	All eligible participants were included in the study, and start of follow up coincided with start of intervention	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to selection of participants into the study?	N/A – no formal hypothesis tested for	-		
Bias in classification of interventions				
3.1 Were intervention groups clearly defined?	A list of relevant interventions was pre-specified, and treatment setting was clearly defined. Specific details such as dose and frequency, were not defined	**PY**	**PY** Treatment doses will be in accordance with NICE recommendations and the respective marketing authorisations	**PY** Treatment doses will be in accordance with NICE recommendations and the respective marketing authorisations
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	A list of relevant interventions was pre-specified	**Y**	**Y**	**Y**
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Intervention status was classified as part of the NCRAS[22] database, independently of outcome assessment	**N**	**N**	**N**
Risk of bias judgement	Intervention status is well-defined and classified upon input into database (i.e., independently of those with knowledge of treatment outcomes)	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to classification of interventions?	N/A – no formal hypothesis tested for	-		
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 – deviations beyond those expected in usual practice are not expected	**N**	**N**	**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?	N/A	-		
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?	N/A	-		
4.4. Was the intervention implemented successfully for most participants?	N/A	-		
4.5. Did study participants adhere to the assigned intervention regimen?	N/A	-		
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?	N/A	-		
Risk of bias judgement	Any potential deviations from intervention would reflect usual practice	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	N/A – no formal hypothesis tested for	-		
Bias due to missing data				
5.1 Were outcome data available for all, or nearly all, participants?	Outcome data were available for all patients but certain data, i.e. baseline characteristics, were missing for some patients	**PY**	**PY** However, the number of patients lost to follow up was not reported	**PY** However, the number of patients lost to follow up was not reported
5.2 Were participants excluded due to missing data on intervention status?	Intervention received formed part of the study eligibility criteria	**N**	**N** Intervention was actively assigned by the treating physician as part of the NHS treatment pathway and was unlikely to be recorded incorrectly or inaccurately	**N** Intervention was actively assigned by the treating physician as part of the NHS treatment pathway and was unlikely to be recorded incorrectly or inaccurately

5.3 Were participants excluded due to missing data on other variables needed for the analysis?	To avoid introducing selection bias, patients were not excluded due to missing data. Instead, where missing data are present, the proportion of missingness was described	**N**	**N**	**N**
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?	-	N/A		
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?	-	N/A		
Risk of bias judgement	All patients had outcome data reported and no patients were excluded from the analysis based on missing data	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to missing data?	N/A – no formal hypothesis tested for	-		
Bias in measurement of outcomes				
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Both outcomes, OS and TTNT, involve negligible assessor judgement (i.e., lack subjectivity)	**N**	**N**	**N**
6.2 Were outcome assessors aware of the intervention received by study participants?	Outcome assessors were not blind to intervention status. However, both outcomes involve negligible assessor judgement	**Y**	**Y**	**Y**
6.3 Were the methods of outcome assessment comparable across intervention groups?	Methods for outcome assessment were pre-specified, and unchanged regardless of intervention received	**Y**	**Y**	**Y**
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Given the nature of outcomes assessed, systematic errors in outcome measurement are not expected	**N**	**N**	**N**
Risk of bias judgement	Both outcomes involve negligible assessor judgement so risk of bias is expected to be low	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to measurement of outcomes?	N/A – no formal hypothesis tested for	-		

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?	Only single outcome measurements within a domain were collected	**N**	**N**	**N**
7.2 ... multiple *analyses* of the intervention-outcome relationship?	Both outcomes, OS and TTNT, were calculated using Kaplan-Meier estimator. No additional analyses were conducted	**N**	**N**	**N**
7.3 ... different *subgroups*?	No subgroups were pre-specified	**N**	**N**	**N**
Risk of bias judgement	Outcome measurements and analyses clearly pre-specified. The study did not involve conducting multiple outcome measurements and analyses so risk of selective reporting unlikely	**Low**	**Low**	**Low**
Optional: What is the predicted direction of bias due to selection of the reported result?	-			
Overall bias				
Risk of bias judgement	Risk of bias judged to be low for 6/7 domains of bias. Only risk of bias due to confounding was judged to be serious, although this is expected given the nature of the study	**Serious**	**Serious**	**Serious**
Optional: What is the overall predicted direction of bias for this outcome?	N/A – no formal hypothesis tested for	-		

[a] The responses to each signally question on the ROBINS-I tool[26] are either, 'yes', 'probably yes', 'probably no', 'no' or 'no information'.
[b] The ROBINS-I tool[26] step 3 to step 6 of the assessment should be completed separately for each key outcome
CS=company submission; EAG=external assessment group; N=no; N/A=not applicable; NCRAS=National Cancer Registration and Analysis Service; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; OS=overall survival; PN=probably no; PY=probably yes; 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; Y=yes
Source: CS, Appendix D.2.6, Table 2

8.3 Appendix 3 EAG revisions to the company clarification model

All revisions should be made to the company clarification model.

EAG revision	Implementation instructions
Set up EAG revision switches and adjustment to stop TTD being greater than PFS	**In Sheet 'Deterministic Results'** Set cell P3="R1" Name cell Q3= EAG_R1" Set cell P4="R2" Name cell Q4="EAG_R2" Set cell P5="R3" Name cell Q5="EAG_R3" Set cell P6="R4" Set cell Q6="Change manually" Set cell P7="R5" Name cell Q7="EAG_R5" Set cell P8="R6" Name cell Q8="EAG_R6" Set cell P9="R7" Name cell Q9="EAG_R7" Set cell P10="S1" Name cell Q10="S1" Name cell P11="S2" Set cell Q11="EAG_S2" Name cell P12="S3" Set cell Q12="EAG_S3" Name cell P13="S4" Set cell Q13="EAG_S4" Name cell P14="S5" Set cell Q14="EAG_S5" Name cell P15="S6" Set cell Q15="EAG_S6" **In Sheet 'Engine (Teclistamab)'** **Set cell T21= Min(TTTD!G19,J21)** **Copy cell T21** **Paste to range T22:T2108**
R1) OS and PFS for patients treated with PomDex attenuated to meet the mid-point of the company clinical expert likely values at 10 and 15 years	**In Sheet 'Deterministic Results'** Set cell Q3 = 1 **In Sheet 'Clinical Inputs'** Set H30 =IF(or(EAG_R1=1,EAG_S1=1,EAG_S2=1,EAG_S5=1,EAG_S6=1),"Yes","No") Set H35 =IF(or(EAG_R1=1,EAG_S1=1,EAG_S2=1,EAG_S5=1,EAG_S6=1),"Yes","No")
R2) TTD for patients treated with teclistamab and PomDex attenuated to meet the mid-	**In Sheet 'Deterministic Results'** Set cell Q4 = 1

EAG revision	Implementation instructions
point of the company clinical expert likely values at 10 and 15 years	**In Sheet 'Clinical Inputs'** Set cell H25 =IF(or(EAG_R2=1,EAG_S3=1,EAG_S4=1,EAG_S5=1,EAG_S6=1),"Yes","No") Set cell H40 =IF(or(EAG_R2=1,EAG_S3=1,EAG_S4=1,EAG_S5=1,EAG_S6=1),"Yes","No")
R3) Switching to Q2W for patients treated with teclistamab occurs at 12 months and follows the proportions switching in the MajesTEC-1 trial from that time point	**In Sheet 'Deterministic Results'** Set cell Q5 = 1 **In Sheet 'TTTD'** Set cell R19=IF(EAG_R3=1,0,P19-Q19) Copy cell R19 Paste to R20:R70
R4) The same utility values for patients treated with teclistamab and PomDex are used, namely the time-dependent utility values from the MajesTEC-1 trial for PFS and the MajesTEC-1 trial value for PD	**In Sheet 'Utility Inputs'** Set cell H10 to "Time dependent utility"
R5) Remove adverse event disutilities	**In Sheet 'Deterministic Results'** Set cell Q7 = 1 **In Sheet 'Utility Inputs'** Copy range M51:M66 Paste values in range R51:R66 Set cell L51=IF(EAG_R5=1,0,R51) Copy cell L51 Paste to L52:L66
R6) Proportion of patients treated with teclistamab receiving subsequent therapy from MajesTEC-1 trial	**In Sheet 'Deterministic Results'** Set cell Q8 = 1 **In Sheet 'Cost Inputs_others'** Set cell F73 =IF(EAG_R6=1,0.7,20/38)
R7) Proportion receiving subsequent therapy in both model arms based on UK RW TCE RRMM cohort study	**In Sheet 'Deterministic Results'** Set cell Q9 = 1

EAG revision	Implementation instructions
	In Sheet 'Cost Inputs_others' Set cell F46 =IF(EAG_R7=1,I46*(1-G55), CHOOSE(i_subs_tx_source,M46,N46,N46)) Copy cell F46 Paste values to range F47:F60 Set cell F55=G55
S1 and S2 as R1 with lower and upper likely values, respectively	**In Sheet 'Deterministic Results'** For S1, Set cell Q10 = 1 For S2, Set cell Q11 = 1 **In Sheet 'Clinical Inputs'** Set cell I16=IF(OR(EAG_S1=1,EAG_S5=1),0.05,IF(OR(EAG_S2=1,EAG_S6=1),0.15,0.1)) Set cell I17=IF(OR(EAG_S1=1,EAG_S5=1),0.01,IF(OR(EAG_S2=1,EAG_S6=1),0.05,0.03)) Set cell I21=IF(OR(EAG_S1=1,EAG_S5=1),0.02,IF(OR(EAG_S2=1,EAG_S6=1),0.08,0.05)) Set cell I22=IF(OR(EAG_S1=1,EAG_S5=1),0.00,IF(OR(EAG_S2=1,EAG_S6=1),0.02,0.01)) Set cell I31=IF(OR(EAG_S1=1,EAG_S6=1),0.00,IF(OR(EAG_S2=1,EAG_S5=1),0.05,0.025)) Set cell I32=IF(OR(EAG_S1=1,EAG_S6=1),0.00,IF(OR(EAG_S2=1,EAG_S5=1),0.01,0.005)) Set cell I36=IF(OR(EAG_S1=1,EAG_S6=1),0.00,IF(OR(EAG_S2=1,EAG_S5=1),0.05,0.025)) Set cell I37=IF(OR(EAG_S1=1,EAG_S6=1),0.00,IF(OR(EAG_S2=1,EAG_S5=1),0.00,0.0))
S3 and S4 as R2 with lower and upper likely values, respectively	**In Sheet 'Deterministic Results'** For S3, Set cell Q12 = 1 For S4, Set cell Q13 = 1 **In Sheet 'Clinical Inputs'**

EAG revision	Implementation instructions
	Set cell I26=IF(OR(EAG_S3=1,EAG_S6=1),0.01,IF(OR(EAG_S4=1,EAG_S5=1),0.05,0.03)) Set cell I27=IF(OR(EAG_S3=1,EAG_S6=1),0.00,IF(OR(EAG_S4=1,EAG_S5=1),0.02,0.01)) Set cell I41=IF(OR(EAG_S3=1,EAG_S5=1),0.00,IF(OR(EAG_S4=1,EAG_S6=1),0.03,0.015)) Set cell I42=IF(OR(EAG_S3=1,EAG_S5=1),0.00,IF(OR(EAG_S4=1,EAG_S6=1),0.00,0.00))
S3 and S4 as R2 with lower and upper likely values, respectively	**In Sheet 'Deterministic Results'** For S3, Set cell Q12 = 1 For S4, Set cell Q13 = 1 **In Sheet 'Clinical Inputs'** Set cell I26=IF(OR(EAG_S3=1,EAG_S6=1),0.01,IF(OR(EAG_S4=1,EAG_S5=1),0.05,0.03)) Set cell I27=IF(OR(EAG_S3=1,EAG_S6=1),0.00,IF(OR(EAG_S4=1,EAG_S5=1),0.02,0.01)) Set cell I41=IF(OR(EAG_S3=1,EAG_S5=1),0.00,IF(OR(EAG_S4=1,EAG_S6=1),0.03,0.015)) Set cell I42=IF(OR(EAG_S3=1,EAG_S5=1),0.00,IF(OR(EAG_S4=1,EAG_S6=1),0.00,0.00))

EAG=External Assessment Group; OS=overall survival; PD=progressed disease; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; Q2W=once every two weeks; RW TCE RRMM=real-world triple-class exposed relapsed or refractory multiple myeloma; TTD=time to treatment discontinuation

EAG ADDENDUM 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Teclistamab for treating relapsed or refractory multiple myeloma after three treatments (Review of TA869) [ID6333]

Addendum to EAG report

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165522

CONTAINS COMMERCIAL IN CONFIDENCE DATA

Date completed 8 May 2024

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

To inform the National Institute for Health and Care Excellence Single Technology Appraisal process of the clinical and cost effectiveness of teclistamab for treating relapsed or refractory multiple myeloma after three treatments, the company (Janssen) presented cost effectiveness results generated by a model developed in MS Excel.

Whilst compiling the confidential appendix (post FAC), the EAG identified an error in the company's estimation of teclistamab costs. In the CS, the company stated that [redacted] missed a dose of teclistamab during the loading phase of the MajesTEC-1 trial but during the maintenance phase, [redacted]% of teclistamab doses were skipped. However, in the company model, a skipped dose value of [redacted]% was used (the percentage of all doses [loading and maintenance] that were missed). Instead of [redacted]%, the EAG has used the company's skipped dose value to [redacted]% (CS, p158) and applied this during the maintenance phase only. The EAG had generated corrected deterministic (Table 1) and probabilistic (Table 2) cost effectiveness results for the company base case analysis and the EAG revisions to the company model, the EAG preferred base case and EAG scenarios.

Table 1 EAG corrected deterministic results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions to company base case	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)		
A. Company clarification base case	[redacted]								
EAG corrected company clarification base case	[redacted]								
R1) Attenuate PomDex OS and PFS (mid-point)	[redacted]								
R2) Use lognormal for teclistamab TTD and attenuate TTD for teclistamab and PomDex (mid-point)	[redacted]								
R3) Patients treated with teclistamab switch from a Q1W to a Q2W regimen at 12 months; no patients switch earlier than 12 months	[redacted]								
R4) PomDex utility values equal teclistamab utility values	[redacted]								
R5) Remove AE disutilities	[redacted]								
R6) MajesTEC-1 trial proportion of patients treated with teclistamab receiving subsequent treatment	[redacted]								
R7) UK RW TCE RRMM PomDex cohort study proportion of patients receiving subsequent treatment (both model arms)	[redacted]								
B. EAG preferred base case (R1-R7)	[redacted]								
EAG scenarios									
S1) Attenuate teclistamab and PomDex OS and PFS using clinician lower likely values	[redacted]								
S2) Attenuate teclistamab and PomDex OS and PFS using clinician higher likely values	[redacted]								
S3) Attenuate TTD using clinician lower likely values	[redacted]								
S4) Attenuate TTD using clinician higher likely values	[redacted]								
S5) Teclistamab optimistic scenario	[redacted]								
S6) Teclistamab pessimistic scenario	[redacted]								

* Willingness to pay threshold=£30,000/QALY

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; Q1W=every week; Q2W=every 2 weeks; QALY=quality adjusted life year; RW TCE RRMM=real-world triple-class exposed relapsed or refractory multiple myeloma; TTD=time to treatment discontinuation

Table 2 EAG corrected probabilistic cost effectiveness results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions[†]	Teclistamab		PomDex		Incremental		ICER	NMB[*]	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 multiplier)	£/QALY		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A1. Company clarification base case with PSA corrected[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred base case (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
† The EAG PSA runs exclude variation of unit costs
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PomDex=pomalidomide plus low-dose dexamethasone PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

EAG ADDENDUM 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Teclistamab for treating relapsed or refractory multiple myeloma after three treatments (Review of TA869) [ID6333]

Addendum 2

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165522

CONTAINS COMMERCIAL IN CONFIDENCE DATA

Date completed 24 May 2024

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP
A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

To inform the National Institute for Health and Care Excellence Single Technology Appraisal process of the clinical and cost effectiveness of teclistamab for treating relapsed or refractory multiple myeloma after three treatments, the company (Janssen) presented cost effectiveness results generated by a model developed in MS Excel.

To inform their submission, the company asked three clinical experts for OS, PFS and TTD estimates at 5, 10 and 15 years for patients treated with teclistamab or treated with PomDex. Each of the three experts provided a *lowest* plausible value, a *most* plausible value and a *highest* plausible value. The company used the mid-point of the range of *most* plausible values for calibration purposes in their economic model. The EAG then produced pessimistic and optimistic scenarios based upon the lowest and highest range of *most* plausible values provided by the three clinicians.

Following the pre-ACM1 PMB, NICE asked the EAG to produce results from two additional scenarios:

- most optimistic scenario: biggest difference in patient outcomes and lowest difference in treatment costs between teclistamab and PomDex
- most pessimistic scenario: smallest difference in patient outcomes and biggest difference in treatment costs between teclistamab and PomDex

When producing these results, the EAG identified that revision R2 had not previously been fully implemented by the EAG, i.e., the distribution used to model teclistamab TTD had not been changed to the lognormal distribution. This correction affects R2 cost effectiveness results, the EAG preferred base case and EAG scenarios 5 and 6. EAG cost effectiveness results are presented in Table 1 (deterministic) and Table 2 (probabilistic); the latest teclistamab PAS (received 22 May 2024) price has been used to generate these results.

Table 1 EAG deterministic results for teclistamab versus PomDex, PAS price for teclistamab (x 1.2 modifier)

EAG revisions to company base case	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY		
A. Company clarification base case†	[redacted]								
A1. EAG corrected company clarification base case†	[redacted]								
R1) Attenuate PomDex OS and PFS (mid-point)	[redacted]								
R2) Use lognormal for teclistamab TTD and attenuate TTD for teclistamab and PomDex (mid-point)	[redacted]								
R3) Patients treated with teclistamab switch from a Q1W to a Q2W regimen at 12 months; no patients switch earlier than 12 months	[redacted]								
R4) PomDex utility values equal teclistamab utility values	[redacted]								
R5) Remove AE disutilities	[redacted]								
R6) MajesTEC-1 trial proportion of patients treated with teclistamab receiving subsequent treatment	[redacted]								
R7) UK RW TCE RRMM PomDex cohort study proportion of patients receiving subsequent treatment (both model arms)	[redacted]								
B. EAG preferred base case (R1-R7)	[redacted]								
EAG scenarios									
S1) Attenuate teclistamab and PomDex OS and PFS using clinician lower likely values	[redacted]								
S2) Attenuate teclistamab and PomDex OS and PFS using clinician higher likely values	[redacted]								
S3) Attenuate TTD using clinician lower likely values	[redacted]								
S4) Attenuate TTD using clinician higher likely values	[redacted]								
S5) Teclistamab optimistic scenario (R1-R7)	[redacted]								
S6) Teclistamab pessimistic scenario (R1-R7)	[redacted]								
S7) Requested by NICE: most optimistic scenario (R1-R7)	[redacted]								
S8) Requested by NICE: most pessimistic scenario (R1-R7)	[redacted]								

* Willingness to pay threshold=£30,000/QALY

† Does not include R5, R6 and R7 which were accepted by the company in the company addendum

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; Q1W=every week; Q2W=every 2 weeks; QALY=quality adjusted life year; RW TCE RRMM=real-world triple-class exposed relapsed or refractory multiple myeloma; TTD=time to treatment discontinuation

Table 2 EAG probabilistic cost effectiveness results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions‡	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 multiplier)	£/QALY		
A. Company clarification base case†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A1. EAG corrected company clarification base†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred base case (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7) Requested by NICE: most optimistic scenario (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8) Requested by NICE: most pessimistic scenario (R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
‡ The EAG PSA runs exclude variation of unit costs
† Does not include R5, R6 and R7 which were accepted by the company in the company addendum
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PomDex=pomalidomide plus low-dose dexamethasone PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

EAG ADDENDUM 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Teclistamab for treating relapsed or refractory multiple myeloma after three treatments (Review of TA869) [ID6333]

Addendum 3

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165522

CONTAINS COMMERCIAL IN CONFIDENCE DATA

Date completed 31 May 2024

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

To inform the National Institute for Health and Care Excellence Single Technology Appraisal process of the clinical and cost effectiveness of teclistamab for treating relapsed or refractory multiple myeloma after three treatments, the company (Janssen) presented cost effectiveness results generated by a model developed in MS Excel.

The company produced a new base case and presented this as part of the clarification response. The clarification model used a higher estimate for skipped doses ([redacted]) for teclistamab than the original company base case model ([redacted]). In the clarification response, the company provided the rationale for this change. The EAG originally considered that this was reasonable; however, on further reflection, the EAG considered that this change was not appropriate. The EAG submitted an addendum (8 May 2024); results in this addendum reflected the EAG's view that the change to the higher estimate was an error.

In the 8 May 2020 addendum, EAG revisions to the company base case were not made to the company clarification base case (high estimate of skipped doses), they were made to the EAG corrected clarification company base case (low estimate of skipped doses). The EAG now recognises that rather than correcting the company clarification base case, the EAG should have included an additional revision to the company clarification base case (i.e., implementing the low estimate rather than the high estimate of skipped doses).

In the MajesTEC-1 trial CSR (pp431-432), the mean and median dose intensities varied between maintenance treatment cycles (mean: [redacted]% to [redacted]%; median: [redacted]% to [redacted]%) and overall mean and overall median dose intensities were reported as [redacted]% and [redacted]% respectively. Whilst dose intensity may not have been calculated by the company in the same way as skipped doses, the EAG considers the dose intensity estimates reported in the CSR support a skipped dose estimate of [redacted] more than an estimate of [redacted].

The specific points raised by the company to justify their amended skipped doses calculation at clarification were:

Company point 1: Patients with dose delays were not recorded as skipped doses in the trial.

EAG response: Delays should not have been (and were not) recorded in the MajesTEC-1 trial as skipped doses. Delayed doses are not the same as missed doses and should not be included in the skipped dose calculation.

Company point 2: The number of expected doses was based on the date of treatment discontinuation (for patients who discontinued treatment) or last trial observation (for patients with ongoing treatment at the time of the data cut).

EAG response: In a trial, time to treatment discontinuation is measured as the time between a patient's first dose and a patient's last dose. In the original company model, the company used this measure to estimate missed doses; the EAG considers this is the correct approach.

Company point 3: Difference in permitted teclistamab dose frequency in the MajesTEC-1 trial compared to the teclistamab licence wording.

EAG response: In the MajesTEC-1 trial, teclistamab dosing was permitted weekly, bi-weekly, monthly or bi-monthly; over time, patients could switch to a less frequent (planned) dosing schedule. When calculating the clarification model skipped dose estimate, the company has assumed that trial patients who received teclistamab monthly or bi-monthly did in fact skip doses as the teclistamab licence only permits weekly and bi-weekly dosing. The EAG considers that this approach is not appropriate; if the teclistamab licensed dosing schedule had been implemented in the MajesTEC-1 trial, the effects on time on treatment, skipped doses and outcomes are unknown.

1.1 EAG updated cost effectiveness results

In the addendum to the EAG report (8 May 2024), the EAG incorrectly reported the change in the skipped dose estimate as an error. The EAG should have described the change as an EAG revision to the company clarification model rather than as an error.

Table 1 EAG deterministic results for teclistamab versus PomDex, PAS price for teclistamab (x 1.2 modifier)

EAG revisions to company base case	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY		
A. Company clarification base case†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Attenuate PomDex OS and PFS (mid-point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Use lognormal for teclistamab TTD and attenuate TTD for teclistamab and PomDex (mid-point)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) Patients treated with teclistamab switch from a Q1W to a Q2W regimen at 12 months; no patients switch earlier than 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) PomDex utility values equal teclistamab utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5) Remove AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R6) MajesTEC-1 trial proportion of patients treated with teclistamab receiving subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R7) UK RW TCE RRMM PomDex cohort study proportion of patients receiving subsequent treatment (both model arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred base case (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenarios									
S1) Attenuate teclistamab and PomDex OS and PFS using clinician lower likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S2) Attenuate teclistamab and PomDex OS and PFS using clinician higher likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3) Attenuate TTD using clinician lower likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4) Attenuate TTD using clinician higher likely values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7) Requested by NICE: most optimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8) Requested by NICE: most pessimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

† Does not include R5, R6 and R7 which were accepted by the company in the company addendum

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PomDex=pomalidomide plus low-dose dexamethasone; Q1W=every week; Q2W=every 2 weeks; QALY=quality adjusted life year; RW TCE RRMM=real-world triple-class exposed relapsed or refractory multiple myeloma; TTD=time to treatment discontinuation

Table 2 EAG probabilistic cost effectiveness results for teclistamab versus PomDex, PAS price for teclistamab

EAG revisions‡	Teclistamab		PomDex		Incremental		ICER	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 multiplier)	£/QALY		
A. Company clarification base case†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
B. EAG preferred base case (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5) Teclistamab optimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6) Teclistamab pessimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7) Requested by NICE: most optimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8) Requested by NICE: most pessimistic scenario (company original base case, R1-R7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
‡ The EAG PSA runs exclude variation of unit costs
† Does not include R5, R6 and R7 which were accepted by the company in the company addendum
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PomDex=pomalidomide plus low-dose dexamethasone PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

Addendum to Company submission (includes EAG response)

May 2024

File name	Version	Contains confidential information	Date
ID6333_Teclistamab_Addendum_V1.0 [CON].docx	1.0	Yes	21 May 2024

Introduction

Johnson & Johnson Innovative Medicine (previously Janssen) would like to thank NICE for accepting this short addendum to the Company submission. The purpose of this addendum is to provide additional scenarios around the use of therapeutic immunoglobulin in patients treated with teclistamab. This is to support Committee decision making by exploring the impact that variations in therapeutic immunoglobulin use may have on the incremental cost-effectiveness of teclistamab. These scenarios are presented in Section B1.

In addition, Johnson & Johnson Innovative Medicine have amended the company base case to further align with the EAG base case (see Section A) and presented additional evidence on the topic of drug wastage gathered from early use of teclistamab in the UK in the single patient request programme (see Section B2).

We hope that this addendum is useful to support a recommendation for teclistamab in the triple-class exposed, relapsed refractory multiple myeloma patient population addressing the critical unmet need for treatments that may prolong survival and improve quality of life.

Section A: Change(s) to the Company's base case

In addition to this addendum, Johnson & Johnson Innovative Medicine have submitted an updated confidential simple patient access scheme (PAS) of [redacted] for teclistamab. The impact of this updated PAS on the base case Company results is presented in Table 1 below. This leads to a change in the Company base case INHB of [redacted]. All subsequent results presented in this addendum take into consideration this updated PAS.

Table 1. Impact of updated PAS on Company base case results (deterministic, TEC PAS price, 1.2x severity modifier applied)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case Incremental Costs	Δ from Base Case Incremental QALYs	Δ from Base Case INHB
Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Company clarification base case with updated PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue 7: Application of a one-off utility decrement for patients who experience TEAEs represents double counting

The Company base case included adverse event disutilities. Utility decrements due to AEs were sourced from publications and previous HTA submissions (see Company submission (CS) Table 51). The duration of utility decrements was based on MajesTEC-1. Utility decrements were applied as one-time decrements in baseline utility value at the start of the partitioned survival model. The EAG base case excluded this adjustment based on the MajesTEC-1 trial HRQoL dataset already including data from patients who experienced AEs.

In response to the EAG report, Janssen has revised the company economic model to remove the TEAE disutility values, and therefore the impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

Key issue 8: Proportion of patients treated with teclistamab who receive subsequent treatment

The Company base case assumed that 52.6% of patients go on to receive a subsequent treatment following disease progression on teclistamab or PomDex based on Djebbari et al. (2020), a real-world study of UK MM patients[1]. This approach is consistent with the Committee's preferred assumptions used in NICE TA889 (cilta-cel appraisal) and NICE TA658 (IsaPomDex appraisal). A scenario was included in the company submission to explore the impact of using MajesTEC-1 trial data to inform the proportion of subsequent treatments in the teclistamab arm, i.e. ([redacted]%)[2] (see CS scenario 8b).

The EAG report considered that the proportion should reflect the experience of the MajesTEC-1 trial teclistamab population rather than on real world study data (i.e., the aforementioned scenario analysis).

While either approach is plausible and may have been accepted in previous appraisals, Janssen has revised the company economic model to update the model according to the EAG preference. The impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

Key issue 9: Subsequent treatments should reflect NHS practice

The Company submission presented all the reasonable adjustments that were taken to ensure that the subsequent treatments costed in the economic model were reflective of NHS practice (see CS, Section B.3.3.2 and Section B.3.5.4).

In both MajesTEC-1 and the UK RW TCE cohorts [2,3], there were instances of patients receiving subsequent regimens which are not routinely available in UK clinical practice (see Table 67 in CS). In order to ensure subsequent treatment costs were reflective of the UK treatment pathway, the subsequent treatment distributions in both studies were re-weighted to remove subsequent treatments not routinely available in the UK and/or after 3 prior therapies e.g. talquetamab, cilta-cel, carfilzomib, belantamab (see Table 68 in CS). Additionally, overall survival in the teclistamab arm was further adjusted using the advanced "two-stage" method described in NICE TSD 16 [4] for the possible effects of subsequent treatments in the MajesTEC-1 trial not currently routinely available in UK clinical practice, which might have the potential to increase the predicted long-term estimates of survival. No OS adjustment was undertaken in the PomDex arm as a conservative approach.

Based on clinical advice that choice of subsequent treatment is unlikely to affect clinical outcomes, the EAG report discarded the empirical MajesTEC-1 trial data and instead equalised the distribution of subsequent treatments received by triple-class exposed relapsed/refractory multiple myeloma (RRMM) patients across both teclistamab or PomDex arms, with the exception

that some patients initially treated with teclistamab receive a proportion of PomDex as a subsequent treatment as observed in the MajesTEC-1 trial ([redacted]%).

While either approach is plausible, and may have been accepted in previous appraisals (e.g. TA889, TA658), Janssen has revised the company economic model to update the distribution of subsequent treatments received by MajesTEC-1 trial patients and PomDex patients in line with the EAG approach. The impact of this change (on its own) results in a [redacted] change in the Company clarification base case deterministic INHB (March 2024).

A summary of the changes to the Company's base case can be found below in Table 2. Combined, key issues 7, 8 and 9 lead to an updated INHB of [redacted] compared to the Company base case INHB of [redacted].

EAG comment:

No comment

Table 2. Summary of change(s) to the Company's clarification base case in response to the EAR (deterministic, updated TEC PAS price, 1.2x severity modifier applied)

Key issue(s) in the EAR that the change relates to	Company's clarification base case before EAR	Change(s) made in response to EAR	Impact on the Company's base-case
Key Issue 7: Application of a one-off utility decrement for patients who experience TEAEs represents double counting	In the original CS, a one-off TEAE disutility was applied in line with literature and previous appraisals (e.g. TA171, TA573, TA559, TA510).	Janssen has updated the economic model to remove TEAE disutility.	Base case INHB (Mar 2024): [redacted] Impact of removing TEAE disutility (May 2024): [redacted]
Key Issue 8: Proportion of patients treated with teclistamab who receive subsequent treatment	In the original CS, the proportion of patients receiving subsequent therapies was assumed to be 52.6% in both teclistamab and PomDex arms, based on a UK RWE report by Djebarri et al (2020) and previous appraisals (TA889, TA658).	Janssen has updated the proportion of subsequent treatments for patients treated with teclistamab ([redacted]%).	Base case INHB (Mar 2024): [redacted] Impact of updating the proportion of subsequent treatments (May 2024): [redacted]
Key Issue 9: Subsequent treatments should reflect NHS practice	In the original CS, the distribution of subsequent treatments was informed by both MajesTEC-1 trial and the UK RW TCE cohort study.	Janssen has updated the distribution (and frequencies) of subsequent treatments so that these are the same for patients treated with teclistamab and PomDex, with further adjustment to the proportion of PomDex as a subsequent treatment for patients treated with teclistamab.	Base case INHB (Mar 2024): [redacted] Impact of adjusting the distribution of subsequent treatments (May 2024): [redacted]
Key issues 7, 8 and 9 combined	-	-	Base case INHB (Mar 2024): [redacted] Updated INHB (May 2024): [redacted]

CS: Company submission; **TA**: Technology appraisal; **TEAE**: treatment-emergent adverse event; **INHB**: incremental net health benefit; **RW/RWE**: real-world evidence; **TCE**: triple-class exposed

Section B: Additional scenarios

B1. Immunoglobulin use

Context

Use of therapeutic immunoglobin, a feature of the teclistamab cost-effectiveness model, has been a topic of discussion in several NICE appraisal committee meetings, including appraisals focused on RRMM treatments. In light of these discussions, and recognising the urgent clinical unmet of the TCE RRMM patients alongside our common objective of obtaining positive access for teclistamab as early as possible, we seek to further support the Committee's decision-making by offering supplementary analyses.

In our original submission and in response to clarification questions, we provided cost-effectiveness model results for scenarios involving lower IVIG use than in the base case. However, we have considered additional scenarios presented below in this addendum to provide further insights into the potential impact on the INHB (through varying costs) when increased IVIG use is considered, to a reasonable upper limit.

Our position is that the use of IVIG as per the base case, which is based on the MajesTEC-1 trial provides the most robust, data-driven evidence for decision making. This is because the efficacy and safety of teclistamab in the economic model are also derived from MajesTEC-1. Thereby, using MajesTEC-1 to inform efficacy, safety and IVIG use ensures internal consistency of the model results. There is a growing body of evidence that usage of IVIG reduces infection with BCMA-targeting bispecifics [5-7]. As correctly noted by the EAG during the clarification stage, it is not reasonable to simply adjust costs or outcomes without adjusting both appropriately; this results in overly optimistic or pessimistic scenarios depending on the direction of adjustment. Thus, we consider the scenarios presented in this addendum a highly conservative approach, given that only costs of additional IVIG use have been modelled without any adjustments to clinical outcomes.

Finaly, we note the scope of this appraisal defines teclistamab as the intervention under question (not teclistamab in combination with IVIG). The evidence provided in the submission and included in the economic model relates to teclistamab as it was studied in MajesTEC-1. Whilst we acknowledge that there is uncertainty regarding the use of IVIG alongside bispecific antibodies, our position is that the clinical and cost-effectiveness of IVIG is a decision problem in its own right and outside the scope of this appraisal. The evidence we have provided is sufficient to demonstrate that teclistamab used as per trial is clinically and cost-effective compared to PomDex. We are keen to avoid scope creep precluding patient access to teclistamab owing to uncertainty regarding use of IVIG, and indeed the cost-effectiveness of IVIG.

Additional Analyses

The SmPC for teclistamab [8] indicates that severe, life-threatening, or fatal infections have been reported in patients receiving teclistamab. Patients should be monitored for signs and symptoms

of infection prior to and during treatment with teclistamab and treated appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines. In case of Grade 3 or greater infections, the SmPC recommends withholding subsequent maintenance doses of teclistamab until infection improves to Grade 2 or better. Immunoglobulin levels should be monitored during treatment with teclistamab and it is noted that immunoglobulin replacement therapy was administered in 39% of patients.

Therapeutic immunoglobulin is recommended to be available as a routinely commissioned treatment option in NHS England for secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment for 6 months and either proven specific antibody failure or serum level of IgG <4 g/L (excl. paraprotein) [9]. If approved by panel, the standard clinical practice is to dose at 0.4g/kg/month and, based on mean bodyweight of [redacted]kg in MajesTEC-1, a dose of 30g would be administered every 4 weeks. Six (6) monthly reviews (compared to baseline) are expected to be documented and an annual review is recommended to assess whether the patient still benefits from Ig treatment. For patients who are more susceptible to seasonal infections (like myeloma patients who are suffer most from respiratory infections), the policy considers appropriate to temporarily cease Ig therapy over the summer months.

In the NHS England budget impact analysis (BIA) submission for teclistamab (Jan 2024), it is acknowledged that the duration of treatment with immunoglobulin is variable and hard to predict. Based on clinical advice received from NHSE, nine (9) administrations were modelled in the BIA. In line with the BIA, the Company presents additional scenarios varying the duration of IVIG use with teclistamab to explore impact of this uncertainty (i.e. 6, 9 and 10 doses) for 2 assumptions on the proportion of patients receiving IVIG, i.e. 39% as per the BIA/SmPC or [redacted]% as per the Company base case (based on MajesTEC-1).

A complete list of the scenarios explored and impact on both the Company base case and the EAG Base case INHB is provided in Table 3 below.

Table 3. Summary of scenario analyses on IVIG use with teclistamab (deterministic, updated TEC PAS price, 1.2x severity modifier applied)

	Description of the scenario	Company clarification base case INHB at £30,000 (including key issues 7, 8 and 9)	EAG base case INHB at £30,000
0	Base case INHB at £30,000	[redacted]	[redacted]
1a	39% patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
1b	39% patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
1c	39% patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]
2a	[redacted]% patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
2b	[redacted]% patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
2c	[redacted]% patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]

IVIG: intravenous immunoglobulin; **EAG**: External Assessment Group; **INHB**: incremental net health benefit

EAG comment

The EAG considers that it is appropriate to understand how changes in IVIG use may impact the cost of treatment with teclistamab but agrees with the company that, without understanding the impact IVIG has on patient outcomes, the real impact of increased IVIG use on the cost effectiveness of teclistamab is unclear.

The EAG has reproduced company Table 3 using net monetary benefit and the EAG corrected company base case (Table 4).

Table 4 EAG summary results of IVIG use with teclistamab scenario analyses (deterministic, updated TEC PAS price, 1.2 x severity modifier applied)

	Description of the scenario	Company clarification base case NMB at £30,000 (including key issues 7, 8 and 9)	EAG preferred base case NMB at £30,000*
0	Base case NMB at £30,000	[redacted]	[redacted]
1a	39% patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
1b	39% patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
1c	39% patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]
2a	[redacted]% patients treated with teclistamab receive 6 doses of IVIG	[redacted]	[redacted]
2b	[redacted]% patients treated with teclistamab receive 9 doses of IVIG	[redacted]	[redacted]
2c	[redacted]% patients treated with teclistamab receive 10 doses of IVIG	[redacted]	[redacted]

IVIG: intravenous immunoglobulin; **EAG**: External Assessment Group; **NMB**: net monetary benefit

* The EAG referred base case includes a correction to a company model error relating to the estimation of teclistamab costs outlined in EAG addendum 1 (dated 8 May 2024) and also includes a correction to EAG revision 2 outlined in EAG addendum 2 (dated 24 May 2024).

B2. Drug wastage

The company submission assumed that drug wastage will be limited in the delivery of teclistamab based on assumption that vial sharing is encouraged by NHS England (TA862, TA819, TA704) and previous appraisals in RRMM where drug wastage assumptions were accepted (TA658).

In the base case, it is considered that vial sharing occurs in NHS practice and therefore, 15% drug wastage for teclistamab is assumed, in line with the NICE appraisal for belantamab mafodotin for treating RRMM after 4 or more therapies (ID2701). Once reconstituted, the shelf life of teclistamab (20 hours) is longer than the shelf-life of belantamab mafodotin (4 hours), so assuming 15% wastage is conservative. The company submission included a scenario exploring the impact of 25% drug wastage for teclistamab.

Since the submission, Janssen has gathered information from the early use of teclistamab in the UK. In the UK single patient request programme (UK SPR), [redacted] TCE RRMM patients received teclistamab in this early access programme between March 2022 and February 2023 [10]. Vial sharing was not permitted, implying that drug wastage in the UK SPR would be higher than it would be in standard UK clinical practice, where vial sharing would be encouraged. Using patient-level data, the volume of drug wastage was estimated to be [redacted]% on maintenance doses ([redacted]% including step-up doses).

This new evidence supports a low drug wastage assumption with teclistamab, even in the conservative scenario where no vial sharing occurs, hence further supporting the base case assumption of drug wastage, and placing a plausible upper bound of ~25%.

EAG comment

In line with the company, the EAG considers that, given the evidence presented by the company, drug wastage is likely to be closer to 15% than 25%.

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5. Leleu X., et al. "P-286 Impact of hypogammaglobulinemia and immunoglobulin replacement therapy on infection rate in patients with RRMM treated with elranatamab: post-hoc analysis from MagnetisMM-3." Clinical Lymphoma Myeloma and Leukemia 23 (2023): S194.
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9. NHS England. Clinical commissioning policy for the use of therapeutic immunoglobulin (Ig) England (2024). 29 April 2024. Available at: https://www.england.nhs.uk/publication/commissioning-criteria-policy-for-the-use-of-therapeutic-immunoglobulin-ig-in-england-2021/ [Last accessed: 21/05/2024]
10. Janssen Data on File. UK Teclistamab single-patient programme (SPR). May 2024

Single Technology Appraisal

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments (Review of TA869) [ID6333]

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 Thursday 25 April 2024** 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 [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Major Issues

Issue 1 Textual amendment or additional wording required in the EAG's critique of the company ITCs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 1A: Textual amendment required in EAG's critique of the company ITCs as methodologically flawed thereby resulting in biased/unreliable/uncertain results			
At multiple points throughout the report, the EAG suggests that the company ITCs are methodologically flawed and consequently, the results are biased, unreliable and/or uncertain. Page 10,12, 53, and 60: *The IPTW method may therefore be unstable, and the estimated treatment effects may be biased and uncertain.* Page 54: '*The EAG considers that the possibility of unstable weights introduces uncertainty into the company's base case analysis results. Although sensitivity analyses results are*	Janssen suggests acknowledging the limitations of the data to inform the indirect treatment comparison, but recognising that the company has explored all options and demonstrated consistency in results across all methodological approaches.	Janssen maintains that the ITCs (base case and sensitivity analyses) are not methodologically flawed and therefore the results of the indirect comparison are not biased in favour of teclistamab, unreliable nor uncertain: • While Janssen acknowledges that the baseline patient characteristics of the MajesTEC-1 and UK RW TCE cohorts were different, the key factor driving the propensity score model is refractory status, (see Appendix 1 of this form). As patients in MajesTEC-1 were more refractory, than the UK RW TCE cohort and the level of refractoriness is prognostic	Thank you for providing the additional information; it has addressed some of the EAG concerns. The information provided by the company in Appendix 1 does not alter the EAG's overall conclusions (i.e., that the company ITC results **may be** biased and uncertain as the company's ITCs were methodologically flawed). The EAG has reviewed the additional methods and results provided in Appendix 3 and Appendix 4 and has made the following changes to the EAR: • the EAG has deleted the following text (EAR, p10): "the IPTW method used was likely

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
similar to base case analysis results, the EAG does not consider that this is reassuring as the methods used to conduct the sensitivity analyses may be as flawed as the methods used to conduct the base case analysis'. Page 55: '*Therefore, the EAG considers the company's use of alternative weighting approaches (ATT, ATE, ATO) in sensitivity analyses was well-justified. However, the EAG does not consider that sensitivity analyses results can be used to demonstrate the robustness of the company base case analysis as the methods used were flawed'*. Page 55 and 60: '*Overall, the EAG considers that the company ITCs are methodologically flawed and results may be unreliable*'.		for worse outcomes, inclusion of these patients from MajesTEC-1 represents a conservative approach. • Sensitivity analyses using ATO and PS matching approaches were presented in the CS; it is widely accepted that these methods are appropriate in circumstances where there are issues with PS overlap (Zhou & Thomas, 2020)[1]. Further, as suggested by the EAG (see issue 1D), in addition to the ATO and PS matching approaches, ATC trimming and truncation scenarios have been presented in Appendix 3 of this form. • All sensitivity analyses (ATO, PS matching, ATC truncation and ATC trimming) produced highly consistent results with the base case (ATC) for both OS and TTNT, demonstrating the robustness of the results.	unstable due to insufficient overlap between cohorts" • the EAG has deleted the following text (EAR, p53): "However, as population overlap was poor prior to adjustment, the IPTW method used to perform the 6-variable and 5-variable adjustments is unstable, and the EAG does not consider that CS, Figure 28 or CS, Figure 30 are informative." • the EAG has added the following text (EAR, pp53-54): "As part of the company's factual accuracy check (FAC), the company provided methodological details for the propensity scores matching sensitivity analyses and the IPTW ATO approach (company FAC, Appendix 4). The company also provided results from additional sensitivity analyses which used the ATC truncation and ATC trimming approach (company FAC,

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		[1]Zhou Y, Matsouaka RA, Thomas L. Propensity score weighting under limited overlap and model misspecification. Stat Methods Med Res 2020;29(12):3721-3756	Appendix 3). Results from these sensitivity analyses (company FAC, Appendix 3, Figure 7 and Figure 8) were similar to those reported in the company base case analysis (CS, Table 28)." • the EAG has deleted the following text (EAR, p54): "However, details of these sensitivity analyses are scarce, and it is not clear what methods were used to assess and adjust for (if necessary) imbalances in covariates post matching. All the other 10 sensitivity analyses employed methods that rely on good overlap between patient populations. The EAG considers that the possibility of unstable weights introduces uncertainty into the company's base case analysis results. Although sensitivity analyses results are similar to base case analysis results, the EAG does not consider that

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			this is reassuring as the methods used to conduct the sensitivity analyses may be as flawed as the methods used to conduct the base case analysis." • The EAG has deleted the following text (EAR, p55): "However, the EAG does not consider that sensitivity analyses results can be used to demonstrate the robustness of the company base case analysis as the methods used were flawed" and added: "Results from these sensitivity analyses were similar to those reported in the company base case analysis" • The EAG has deleted the following text (EAR, p60): "• there was insufficient overlap between the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort prior to population adjustment; this means that the IPTW method used may have been

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			unstable and that consequently, the estimated treatment effects may be biased and uncertain • the company did not trim or match the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort; this approach could have been used to improve overlap" • The EAG has deleted the following text (EAR, p82): "The EAG considers that the IPTW method used by the company was likely to be unstable due to insufficient overlap of patient cohorts."
Issue 1B: Additional wording for clarity required in EAG's critique of the ITCs regarding patient weighting			
Page 53 In Section 3.5.5 (EAG critique of company indirect comparisons), the EAG report states '*Considering the company's assessment of overlap prior to population adjustment, the EAG*	Janssen suggests the second and third sentences are amended as per below: *'An important issue arises if there are problems with overlap i.e., predicted propensity scores may be close to zero, leading to*	Janssen has provided a detailed breakdown of the distribution of weights in the MajesTEC-1 cohort in Appendix 2 of this form (Table 2). As outlined in the table, in the base case analysis using ATC weights, only one patient in the MajesTEC-1 cohort	Thank you for providing the additional information; it has addressed some of the EAG concerns. The information provided by the company in Appendix 2 does not change the EAG's original

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
notes that SMDs were >0.25 for all six adjustment variables, which signals problems with overlap between populations. An important issue arises if there are problems with overlap i.e., predicted propensity scores may be close to zero, leading to excessively large weights (as weights were calculated by taking the inverse of propensity scores). The IPTW method may therefore be unstable, and the estimated treatment effects may be biased.'	*excessively large weights (as weights were calculated by taking the inverse of propensity scores).* ***However, in the company base case which uses ATC weights, only one patient in the MajesTEC-1 cohort received a weight above 6. The sensitivity of the comparative results by capping the weight of this patient is very small, demonstrated by the consistency of results using truncation and trimming.*** ~~*The IPTW method may therefore be unstable, and the estimated treatment effects may be biased*~~.'	received a weight above 6. The sensitivity of the comparative results by capping the weight of this patient is very small, demonstrated by the consistency of results using truncation and trimming. Thus, the issue highlighted by the EAG that '*there are problems with overlap i.e., predicted propensity scores may be close to zero, leading to excessively large weight'* is not observed in the base case analysis. This should be reflected in the EAG's critique of the company ITC as per the suggested amendments.	conclusion (EAR, p60) that "there was insufficient overlap between the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort prior to population adjustment." The EAG has acknowledged the company's additional sensitivity analyses in the EAR (see EAG response to Issue 1).
Issue 1C: Additional wording for clarity required in EAG's critique of the ITCs regarding patient weighting propensity scores used to assess extent of overlap between populations			
Page 53 In Section 3.5.5 (EAG critique of company indirect comparisons), the EAG report states '*According to the company's histogram, over 50% of patients*	Janssen suggests the first sentence is amended as per below: *'According to the company's histogram,* ***prior to the 6-variable adjustment****, over 50% of patients in the UK RW TCE*	Janssen would like to clarify two points: 1. The histogram referenced by the EAG (i.e., CS Figure 27) refers to the distribution of PSs <u>before</u> weighting for patients (6-variable	Thank you for clarifying that the propensity scores presented in CS, Figure 27 for the UK RW TCE cohort reflect the probability of belonging to the MajesTEC-1 trial population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
in the UK RW TCE RRMM study PomDex cohort have a less than 5% probability of belonging to the UK RW TCE RRMM study PomDex cohort (rather than the MajesTEC-1 trial All Treated Analysis Set population), given their observed characteristics. The EAG considers that these propensity scores are implausible and that it is not appropriate to use the company's histogram to assess the extent of overlap prior to population adjustment.'	*RRMM study PomDex cohort have a less than 5% probability of belonging to the* ***MajesTEC-1 trial*** ~~*UK RW TCE RRMM study PomDex cohort*~~ *(~~rather than the MajesTEC-1 trial All Treated Analysis Set population~~), given their observed characteristics.* ***For the 5-variable adjustment used in the company base case, 12.7% of patients in the UK RW TCE RRMM study PomDex cohort prior to the adjustment have a less than 5% probability of belonging to the MajesTEC-1 trial.***	adjustment) in MajesTEC-1 and the PomDex cohort. Janssen has provided in Appendix 1 the distribution of PSs before weighting for patients (5-variable adjustment) in MajesTEC-1 and the PomDex cohort (Figure 2), which is used in the base case analysis. For this analysis, 12.7% of patients in the UK RW TCE study PomDex cohort have a less than 5% probability of belonging to the MajesTEC-1 trial population prior to the adjustment (Table 1) 2. It appears the EAG has misinterpreted the histogram as reflecting the probability of belonging to the UK cohort for patients in the UK RW TCE RRMM study cohort. Rather, the histogram reflects the probability of belonging to the MajesTEC-1 trial population.	The EAG has deleted the following from the EAG report (page 53): "For each patient from the UK RW TCE RRMM study PomDex cohort, the propensity score indicates the probability that the patient belongs to the UK RW TCE RRMM study PomDex cohort (rather than the MajesTEC-1 trial cohort), given that patient's observed characteristics. For each patient from the MajesTEC-1 trial All Treated Analysis Set population, the propensity score indicates the probability that the patient belongs to the MajesTEC-1 trial All Treated Analysis Set population (rather than the UK RW TCE RRMM study PomDex cohort), given that patient's observed characteristics. According to the company's histogram, prior to the 6-variable adjustment, over 50% of patients in the UK RW TCE RRMM study PomDex cohort have a less than 5% probability of belonging to the UK RW TCE RRMM study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		These clarifications should be reflected on page 53 of the EAG report as per the suggested amendments.	PomDex cohort (rather than the MajesTEC-1 trial All Treated Analysis Set population), given their observed characteristics. The EAG considers that these propensity scores are implausible and that it is not appropriate to use the company's histogram to assess the extent of overlap prior to population adjustment. In addition, the implausibility of propensity scores presented by the company introduces uncertainty into the validity of the calculated MajesTEC-1 trial All Treated Analysis Set population weights."
Issue 1D: Textual amendment required regarding EAG's concern over omission of trimming/matching approach for ITC			
Page 54 In Section 3.5.5 (EAG critique of company indirect comparisons), the EAG report states '*When problems with overlap have been identified, NICE Decision Support Unit Technical Support Document (DSU TSD)*	Page 54: Janssen suggests the final part of the sentence is amended to '~~*the company's base case analyses did not employ either of these methods*~~ **While not provided in the original CS**, **results of the IPTW ATC trimming and truncation analyses were later provided**	Janssen has provided details of the methodology, distribution of propensity scores, SMDs and results of the ATC trimming and ATC truncation sensitivity analyses in Appendix 3 of this form.	Thank you for providing the additional information; it has addressed some of the EAG concerns. The EAG has acknowledged the company's additional sensitivity analyses in the EAR (see EAG response to Issue 1).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
guidance is that trimming of the sample, or matching, should be performed to improve overlap (Figure 3, NICE DSU TSD 17[38]); the company's base case analyses did not employ either of these methods.' Page 60 In Section 3.8.1 (Direct clinical evidence: teclistamab), the EAG report states '*The company did not trim or match the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort; this approach could have been used to improve overlap'*	**by the company and were consistent with the base case analyses results'.** Page 60: Janssen suggests the bullet point is amended to '*The company did not trim or match the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort* ***in the original CS****; this approach could have been used to improve overlap.* **However, updated analyses provided by the company demonstrate that results of the IPTW ATC trimming and truncation analyses were consistent with the base case analyses results'.**	As seen in Figure 7 and Figure 8, results of the IPTW ATC trimming and ATC truncation analyses were consistent with base case for both the OS and TTNT outcomes. Of note, the base case results are the most conservative, suggesting it represents the lower bound of the benefit of teclistamab over PomDex.	The EAG has deleted the following text on p60: "the company did not trim or match the MajesTEC-1 trial cohort and the UK RW TCE RRMM study PomDex cohort; this approach could have been used to improve overlap"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 1E: Textual amendment required regarding EAG's concern over insufficient methodological details of sensitivity analyses (PS matching) presented in the ITC			
Page 54 In Section 3.5.5 (EAG critique of company indirect comparisons), the EAG report states '*When problems with overlap have been identified, NICE Decision Support Unit Technical Support Document (DSU TSD) guidance is that trimming of the sample, or matching, should be performed to improve overlap (Figure 3, NICE DSU TSD 17[38]); the company's base case analyses did not employ either of these methods. Furthermore, the EAG considers that, of the 12 OS sensitivity analyses presented by the company, only two analyses, referred to as "PS matching (c=0.20) – 5 vars" and "PS matching (c=20) – 6 vars" (CS, Figure 33), were likely to have employed methods to improve overlap between the teclistamab and PomDex populations.*	Janssen suggests the final sentence is amended to ***'While not provided in the original CS, details of sensitivity analyses (i.e., PS matching and ATO) were later provided by the company.'***	Janssen has provided details of the methodology, distribution of propensity scores and SMDs related to the PS matching analysis in Appendix 4 of this form. Further, Janssen has provided details of the ATO analysis, which considers the overlapping population between MajesTEC-1 and the UK RW TCE cohorts. This should be reflected on page 54 of the EAG report as per the suggested amendments. Janssen have added functionality within the enclosed model provided as part of this response to explore a number of IPTW approaches. Janssen note that all of the additional IPTW approaches (ATC truncated, ATC trimmed, ATE, ATO, Matching) result in a lower ICER compared to the current EAG and company preferred base case (ATC).	Thank you for providing the additional information; it has addressed some of the EAG concerns. The EAG has acknowledged that the company has provided additional methodological details for these sensitivity analyses (see EAG response to Issue 1A).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
However, details of these sensitivity analyses are scarce, and it is not clear what methods were used to assess and adjust for (if necessary) imbalances in covariates post matching.'			

Issue 2 EAG's methodology to switch teclistamab from a Q1W regimen to a Q2W regimen not aligned with data from MajesTEC-1 and recommendations in the teclistamab Summary of Product Characteristics

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG have updated the dose switching in the CEM such that patients can only switch to the Q2W dosing regimen after 12 months. The argument presented is that this aligns with the SmPC, which states that patients must be in complete response for 6 months before switching to Q2W dosing, and that the mean time to complete response is [redacted] months. This is	Janssen requests that dose switching be amended to occur from [redacted] months instead of from 12 months in the EAG's revised model. Page 11: "Switching patients treated with teclistamab who are on a Q1W regimen to a Q2W regimen from ~~12~~ [redacted] months onwards" Page 14, Issue 4: "The EAG has revised the company model so that patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least ~~12~~ [redacted] months; after ~~12~~ [redacted] months, the	While the mean time to complete response (CR) is [redacted] months, the earliest time observed was [redacted] months (document B, table 16) (with a median [redacted] months). The SmPC states that patients must be in complete response for 6 months or more but it does not provide indication on the time to achieve CR. Janssen therefore believe the EAG's interpretation and model amendment is inaccurate, and that 6 months of	This is not a factual inaccuracy. No change required to the EAG report. The EAG agrees with the company that, as evidenced by MajesTEC-1 trial data, some patients will experience complete response before 6 months and will switch to a Q2W regimen before 12 months. The EAG amendment did not allow switching from a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
referenced in the report document as follows: Page 11: "Switching patients treated with teclistamab who are on a Q1W regimen to a Q2W regimen from 12 months onwards" Page 14, Issue 4: "The EAG has revised the company model so that patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportions who switch at each time point are determined by MajesTEC-1 trial data" Page 14, Issue 4: "The EAG revision decreases the deterministic NMB by £[redacted]" Page 81, Table 34: "Patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportion switching at each	proportions who switch at each time point are determined by MajesTEC-1 trial data" Page 14, Issue 4: "The EAG revision decreases the deterministic NMB by **£[redacted]."** Page 81, Table 34: "Patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least ~~12~~ [redacted] months; after ~~12~~ [redacted] months, the proportion switching at each time point is determined by MajesTEC-1 trial data" Page 85, section 6.5: "The EAG revised the company model so that switching to the Q2W regimen started at ~~12~~ [redacted] months and, from that point onwards, treatment switching reflected the proportion of MajesTEC-1 trial patients who switched to Q2W at different time points, i.e., [redacted]% switched to the Q2W regimen between Week 0 and Week ~~52~~ **32**, and at Week ~~52~~ **33**, [redacted]% of patients still receiving teclistamab switched to Q2W and, from Week ~~53~~ **33** onwards, this proportion increases in line with MajesTEC-1 trial data." Page 87, section 6.9: "Patients treated with teclistamab do not switch from a Q1W to a	complete response could occur far earlier than at the 12 month point. As such, if the EAG would like to amend the company's approach, then patients should be able to switch after [redacted] months (i.e. 6 months + 1.6 months as the earliest time to CR in MajesTEC-1). A modified version of the EAG's model, with an updated Q2W dosing approach, where patients can switch after [redacted] months, is enclosed with this FAC check. To implement the corrected Q2W dose switching (switching allowed from [redacted] months onwards), cell Q5 in sheet 'Deterministic Results' can be set as '2'. This approach is aligned with the SmPC and the data observed in MajesTEC-1.	Q1W to a Q2W regimen until 12 months. From 12 months, the proportions of patients who switched to a Q2W regimen followed the MajesTEC-1 trial switching trajectory. This approach means that some patients who did not achieve a complete response until >6 months of treatment will be assumed to have switched to a Q2W regimen even though they had not achieved a complete response for ≥6 months. Ideally, regimen switching would be modelled using a 6 month shift in the complete response curve (adjusted by the proportion of patients still alive 6 months after complete response). In the absence of these data, it is not clear whether the EAG or company approach provides the best reflection of NHS practice should

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
time point is determined by MajesTEC-1 trial data" Page 85, section 6.5: "The EAG revised the company model so that switching to the Q2W regimen started at 12 months and, from that point onwards, treatment switching reflected the proportion of MajesTEC-1 trial patients who switched to Q2W at different time points, i.e., [redacted]% switched to the Q2W regimen between Week 0 and Week 52, and at Week 52, [redacted]% of patients still receiving teclistamab switched to Q2W and, from Week 53 onwards, this proportion increases in line with MajesTEC-1 trial data." Page 87, section 6.9: "Patients treated with teclistamab do not switch from a Q1W to a Q2W regimen until at least 12 months; after 12 months, the proportions who switch at each time point are	Q2W regimen until at least ~~12~~ [redacted] months; after ~~12~~ [redacted] months, the proportions who switch at each time point are determined by MajesTEC-1 trial data (R3)" Page 89, section 6.9, table 36: "Patients treated with teclistamab switch from a Q1W to a Q2W regimen at ~~12~~ [redacted] months; no patients switch earlier than ~~12~~ [redacted] months" plus NMB change of [redacted]. Page 106, section 8.3, appendix 3: "Switching to Q2W for patients treated with teclistamab occurs at ~~12~~ [redacted] months and follows the proportions switching in the MajesTEC-1 trial from that time point" plus implementation instructions.		teclistamab be recommended by NICE.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
determined by MajesTEC-1 trial data (R3)" See also page 89, section 6.9, table 36 and page 106, section 8.3, appendix 3.			

Issue 3 In the EAG scenario S6, teclistamab TTD exceeds PFS at certain timepoints in the model, which is clinically implausible

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 90 In scenario S6 (teclistamab pessimistic scenario after implementation of R3-R7), the EAG has • Attenuated long term OS and PFS of teclistamab to the lower bound of likely clinical expert values and TTD to the higher likely value.	Janssen suggests acknowledging the limitations of scenario S6 in term of the implications for patients remaining on treatment after progression and revising the statement that "~~*The EAG considers that, given the uncertainty around the comparative efficacy of teclistamab and PomDex and the reliance on clinical expert opinion to estimate long-term outcomes*~~*, the EAG pessimistic scenario cost effectiveness results* ***are not*** ~~*may be the most*~~ *informative*" (EAG report, page 91).	**PFS/TTD** In attenuating long-term teclistamab PFS to the lower bound of likely clinical expert values and TTD to the higher likely value, Janssen notes that TTD exceeds PFS at certain timepoints in the model (Appendix 5, Figure 13; ~[redacted] years to [redacted] years, as PFS does not appear to be capped by TTD in the EAG base case model). For example, at 10 years, TTD is set to the higher clinical expert value at [redacted] and PFS is set to the lower clinical expert value	**PFS/TTD** The EAG has corrected the TTD extrapolation in the pessimistic scenario such that TTD cannot be higher than PFS. The EAR text has been changed in the bullet point describing the pessimistic scenario on p88 to: "teclistamab: long term OS and PFS attenuated

• Attenuated long term OS and PFS of teclistamab to the higher bound of likely clinical expert values and TTD to the lower likely value. Page 91, EAG report: '*The EAG considers that, given the uncertainty around the comparative efficacy of teclistamab and PomDex and the reliance on clinical expert opinion to estimate long-term outcomes, the EAG pessimistic scenario cost effectiveness results may be the most informative'*		at [redacted] Janssen considers this to be clinically implausible i.e., patients remaining on treatment after progressing, given teclistamab is a treat-to-progression drug. In the company base case model, PFS is capped by TTD. If the EAG base case model was to apply this cap, and the pessimistic scenario S6 run, TTD would be equal to PFS for the majority of the model time horizon. Janssen also considers this to be clinically implausible, as patients on teclistamab would not discontinue treatment for the sole reason of disease progression (and/or death) over the entire model time horizon but rather, would discontinue due to other reasons such as adverse events or physician discretion. This is aligned with the SmPC that "*Patients should be treated with TECVAYLI until disease progression or unacceptable toxicity*" and the results of MajesTEC-1. Of the [redacted]% ([redacted]/165) patients who discontinued treatment in MajesTEC-1, the reasons for discontinuation were as follows[3]:	to the lower bound of likely clinical expert values and TTD to the higher likely value or to PFS if PFS is lower than TTD." The EAG pessimistic scenario results have been amended accordingly with instructions on how to cap TTD so that it cannot exceed PFS (EAG report, Appendix 8.3). **<u>OS</u>** The UK RW TCE RRMM study had a data cut-off of March 2023 with median follow up of 26 months and so would also have been impacted by COVID-19. The EAG has inserted the following text to the end of the paragraph of p38: "However, the UK RW TCE RRMM data were also collected during the pandemic and so median OS from the UK RW TCE

		• Progressive disease: [redacted]/165 ([redacted]%) • Death: [redacted]/165 ([redacted]%) • Physician discretion: [redacted]/165 (8.5%) • Adverse event: [redacted]/165 ([redacted]%) • Subject refused further treatment/withdrawal by subject: [redacted]/165 ([redacted]%) • Other (COVID-19% related); [redacted]/165 ([redacted]%) **<u>OS</u>** In the EAG report, it was noted that '*The company considered that median OS may be underestimated as the MajesTEC-1 trial was ongoing during the COVID-19 pandemic;* [redacted] *OS events were deaths due to COVID-19.* ***Clinical advice to the EAG is that this is a reasonable assumption'*** (EAG report, page 38). As OS may already be underestimated by MajesTEC-1, Janssen considers attenuation of long-term OS for teclistamab to the lower bound of	RRMM study may also be underestimated."

		likely clinical expert values to be unreasonable. Thus, for the reasons above, Janssen considers scenario S6 to be implausible and suggests the EAG acknowledge the limitations of this scenario and amend the statement suggesting that this scenario is the most informative for decision-making. [3]MajesTEC_1 CSR: August 2023 CCO, p424	

Minor Issues

Issue 4 Additional wording required in EAG's critique of the proportional hazards (PH) assumption violation introducing further uncertainty in the HRs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 56 In Section 3.5.5 (EAG critique of company indirect	Janssen suggests additional wording is added to the paragraph, as follows:	Despite violation of the PH assumption, Janssen maintains that the overall HR represents the average treatment effect	This is not a factual inaccuracy. No change required.

comparisons), the EAG report states '*The EAG considers that the violation of PH introduces further uncertainty regarding the accuracy of reported HRs for the comparison of teclistamab versus PomDex'*	'*The EAG considers that the violation of PH introduces further uncertainty regarding the accuracy of reported HRs for the comparison of teclistamab versus PomDex.* ***Despite the uncertainty, the reported HRs represent the average treatment effect over the observed time period and as such remain a meaningful measure of the relative effect of teclistamab versus PomDex.****'*	over the observed time period, and this can remain a meaningful measure; this is widely accepted in the literature (Mukhopadhyay 2020)[2]. Janssen note that HRs for the comparison of teclistamab versus PomDex are not utilised in the cost- effectiveness model as extrapolations for both PFS and OS are estimated separately for both cohorts. Therefore, no additional uncertainty is being introduced in the cost effectiveness estimate. [2] Mukhopadhyay, Pralay, et al. *Journal of Biopharmaceutical Statistics* 30.6 (2020): 1130-1146.	

Issue 5 Incorrect reporting of baseline characteristics for real-world teclistamab and PomDex studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 41, Table 9 reports the number of patients with unknown ISS in the Reidhammer German	The number of patients with unknown ISS is not reported in the referenced paper for the Reidhammer study. Furthermore, the number of patients with unknown ISS	To maintain factual accuracy for the real-world studies that results of MajesTEC-1 are being	Thank you for highlighting this. Text amended as suggested and the

retrospective study as “31/123 (25.2)”, however these data were not reported in the given reference. Furthermore, the number of patients in the UK RW TCE RRMM study with the following ISS: “I: 58/216 (26.9) II: 73/216 (33.8) III: 85/216 (39.4)” was given in the EAG report, however these data should be reported from a total patient population of 645 patients, rather than 216.	cannot be assumed to be 31/123 as there is one patient unaccounted for in the total number of patients with ISS of I–III or unknown. Janssen suggests an update to the number of patients with unknown ISS in the Reidhammer study to NR. The number of patients with the ISS of I, II and III in the UK RW TCE RRM study for PomDex are correct, however, there is a total population of 645 patients, rather than 216. This data (and the associated percentages) should be updated accordingly: “I: 58/645 (9.0) II: 73/645 (11.3) III: 85/645 (13.2)”	compared against to ensure fair and accurate comparison.	proportion of UK RW TCE RRMM study PomDex cohort patients with ISS score I, II, III and unknown ISS score are now calculated from the total number of patients rather the number patients with known ISS staging

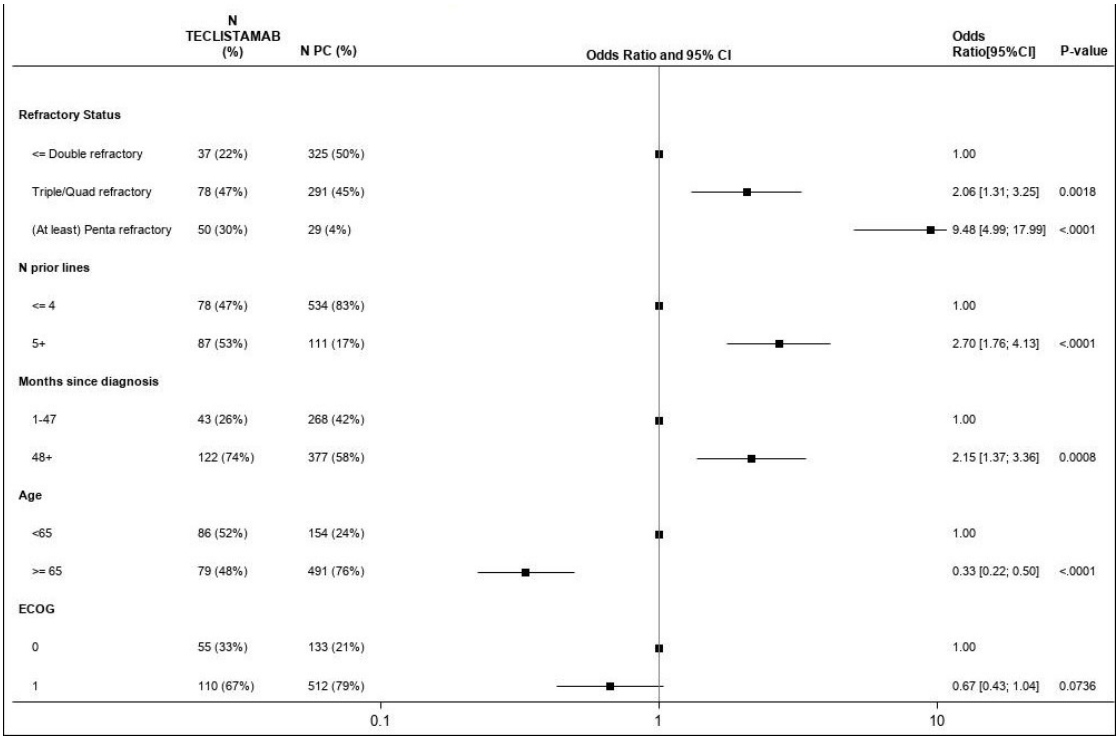
Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, Section 1.4 includes a typographical error in the word 'and': "no adjustments were made for the four priority prognostic factors identified by the company **Tand** the PH assumption was violated for the OS and TTNT comparisons."	Correct the spelling of "**Tand**" to "**and**".	Update the spelling of the typographical error to ensure correct spelling.	Thank you for highlighting this, however, the EAG were unable to find this error in the EAR.
Page 79, the title to section 5 includes a typo in the word 'effectiveness' "5 COST EFFECTIVNESS RESULTS"	Correct spelling of "**EFFECTIVNESS**" to "**EFFECTIVENESS**"	Update the spelling of the typographical error to ensure correct spelling.	Thank you for highlighting this. Text amended as suggested.
Page 12 of the EAG report presents two key issues identified by the EAG, however both issues are identified as "Issue 1".	The issue described in Section 1.3: 'The decision problem: summary of the EAG's key issues' should remain as Issue 1, but the issue described in Section 1.4: 'The clinical effectiveness evidence: summary of the EAG's key issues' should be renamed as "Issue 2". All subsequent key issues identified and described by the EAG should be renumbered accordingly.	To ensure that all key issues are identified by a unique number to avoid confusion when discussing issues.	Thank you for highlighting this. Text amended as suggested.

Page 52, Table 15 in the EAG report reports median OS for teclistamab (post sATC weighting) as [redacted] months.	Median OS for teclistamab (post sATC weighting) should be reported as [redacted] months.	Value should be corrected as per page 105 of Document B of the Company submission.	Thank you for highlighting this. Text amended as suggested.
Page 44, Table 10 in the EAG report reports the percentage of patients achieving a ≥CR (95% CI) in the All Treated Analysis Set of MajesTEC-1 as [redacted].	The percentage of patients achieving a ≥CR (95% CI) in the All Treated Analysis Set of MajesTEC-1 should be reported as [redacted].	Value should be corrected as per page 67 of Document B of the Company submission.	Thank you for highlighting this. Text amended as suggested.
Page 15, Table B in the EAG report lists 'S5) Teclistamab pessimistic scenario' and 'S6) Teclistamab optimistic scenario'	The scenarios should read 'S5) Teclistamab optimistic scenario' and 'S6) Teclistamab pessimistic scenario'	Text should be corrected in Table B to avoid any confusion, as S5 refers to the teclistamab optimistic scenario and S6 refers to the teclistamab pessimistic scenario in all other instances in the EAG report.	Thank you for highlighting this. Text amended as suggested.

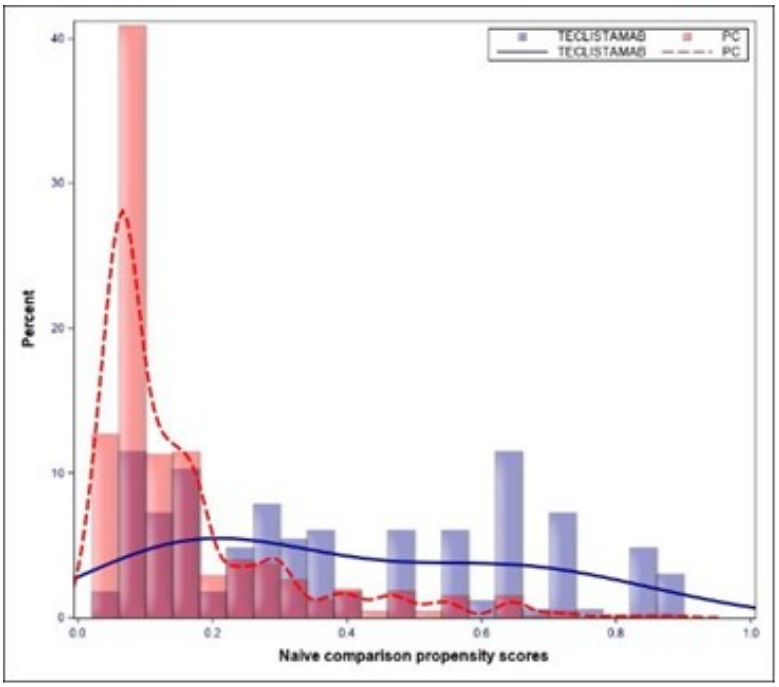
Appendix 1: Base case (IPTW ATC weighting): Propensity score model, and distribution of PSs prior to ATC weighting (5-variable adjustment)

Figure 1. Propensity score model



Source: Janssen Data on File

Figure 2 Distribution of PSs of the observed/unweighted patients prior to 5-variable adjustment (IPTW ATC weighting) for patients in MajesTEC-1 and the PomDex cohort



Source: Janssen Data on File

Table 1. Proportion of patients in MajesTEC-1 and the PomDex cohort with propensity score above and below 0.05

Cohort	Propensity Score above 0.05, n (%)	Propensity Score below 0.05, n (%)	Total N
MajesTEC-1	162 (98.2%)	3 (1.8%)	165
UK RW TCE RRMM PomDex cohort	563 (87.3%)	82 (12.7%)	645
Total (n)	*725*	*85*	*810*

Source: Janssen Data on File

Appendix 2: Base case (IPTW ATC weighting): Distribution of patient weights

Table 2. Distribution of patient weights (IPTW – ATC)

Weight	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0.0322018018	5	3.03	5	3.03

0.0481248459	8	4.85	13	7.88
0.0868044298	1	0.61	14	8.48
0.0966330933	8	4.85	22	13.33
0.1033274946	4	2.42	26	15.76
0.129727207	1	0.61	27	16.36
0.1444159166	12	7.27	39	23.64
0.1478809	7	4.24	46	27.88
0.1863753346	2	1.21	48	29.09
0.2074781798	1	0.61	49	29.70
0.221004575	9	5.45	58	35.15
0.2785336146	6	3.64	64	38.79
0.3051303884	3	1.82	67	40.61
0.3100713273	1	0.61	68	41.21
0.3892931634	1	0.61	69	41.82
0.3986335076	2	1.21	71	43.03
0.4437698515	6	3.64	77	46.67
0.456010288	3	1.82	80	48.48
0.4745126682	1	0.61	81	49.09
0.5957485308	9	5.45	90	54.55
0.6632037499	13	7.88	103	62.42
0.8225213463	4	2.42	107	64.85
0.8558947221	2	1.21	109	66.06
0.9156535232	2	1.21	111	67.27
1.196243277	3	1.82	114	69.09
1.2292390738	2	1.21	116	70.30
1.2791148099	11	6.67	127	76.97
1.368422952	3	1.82	130	78.79
1.4239460016	1	0.61	131	79.39
1.766012304	3	1.82	134	81.21
1.7877578308	9	5.45	143	86.67
2.4682712617	3	1.82	146	88.48
2.5684200844	1	0.61	147	89.09
2.639264426	3	1.82	150	90.91
3.6887741496	8	4.85	158	95.76
3.8384442421	4	2.42	162	98.18
5.29955537	2	1.21	164	99.39
7.9200625783	1	0.61	165	100.00

Source: Janssen Data on File

Appendix 3: ATC trimming and ATC truncation: methodology, SMDs, distribution of propensity scores, and results

Methodology

Truncation

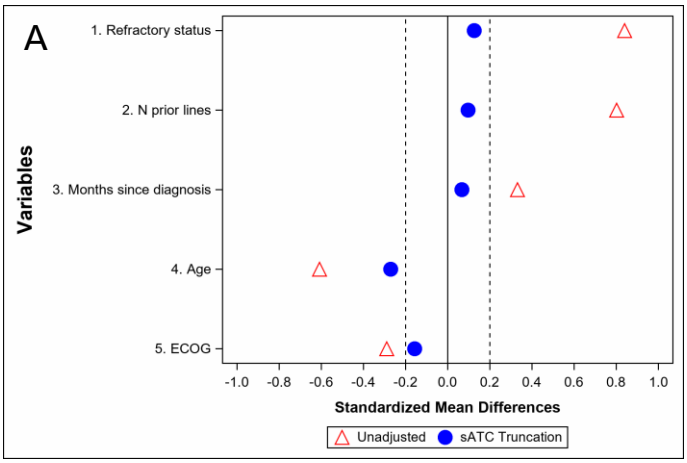
With truncation, ATC weights are truncated by resetting the value of weights lower than 2.5th percentile and greater than 97.5th percentile to the value of 2.5th and 97.5th percentiles (Austin and Stuart 2015)[1]

Trimming

With trimming, patients with a propensity score below the 2.5th percentile of the observed PS in the MajesTEC-1 population and above the 97.5th percentile of the UK RW TCE cohort are left out (Stürmer *et al* 2021)[2]

SMDs and distribution of Propensity Scores (PSs)

Figure 3A and B. SMDs between the MajesTEC-1 and PomDex cohorts after ATC with truncation (percentile cut-offs at 2.5 and 97.5 of PS)



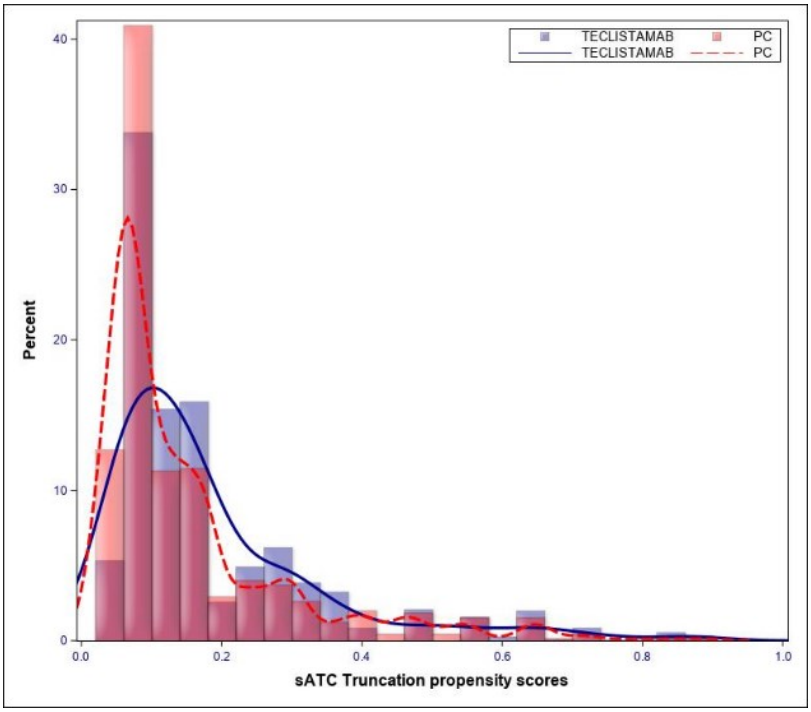
[1] Austin, Peter C., and Elizabeth A. Stuart. *Statistics in medicine* 34.28 (2015): 3661-3679..
[2] Til, et al. "Propensity score weighting and trimming strategies for reducing variance and bias of treatment effect estimates: a simulation study." *American journal of epidemiology* 190.8 (2021): 1659-1670..

B

	TECLISTAMAB	PC	Standardized Difference	Total
Refractory status				
N	139	645	0.1261	784
<= Double refractory	61 (44.1%)	325 (50.4%)		386 (49.3%)
Triple/Quad refractory	70 (50.6%)	291 (45.1%)		361 (46.1%)
(At least) Penta refractory	7 (5.3%)	29 (4.5%)		36 (4.6%)
N prior lines				
N	139	645	0.0962	784
<= 4	110 (79%)	534 (82.8%)		644 (82.1%)
5+	29 (21%)	111 (17.2%)		140 (17.9%)
Months since diagnosis				
N	139	645	0.0669	784
1-47	53 (38.3%)	268 (41.6%)		321 (41%)
48+	86 (61.7%)	377 (58.4%)		463 (59%)
Age				
N	139	645	-0.2696	784
<65	50 (36.1%)	154 (23.9%)		204 (26%)
>= 65	89 (63.9%)	491 (76.1%)		580 (74%)
ECOG				
N	139	645	-0.1569	784
0	38 (27.3%)	133 (20.6%)		171 (21.8%)
1	101 (72.7%)	512 (79.4%)		613 (78.2%)

Source: Janssen Data on File

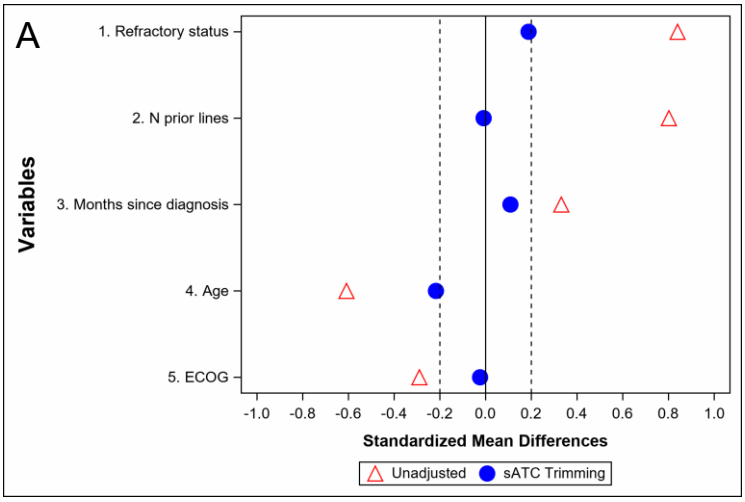
Figure 4. Distribution of PSs after ATC with truncation for patients in MajesTEC-1 and the PomDex cohort



Source: Janssen Data on File

Figure 5A and B. SMDs between the MajesTEC-1 and PomDex cohorts after ATC with trimming (percentile cut-offs at 2.5 and 97.5 of PS)

A

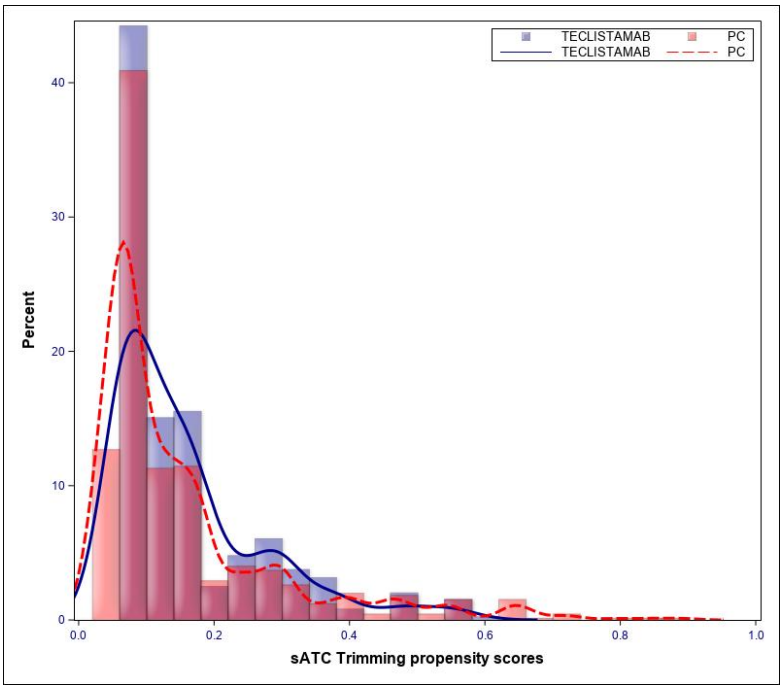


B

	TECLISTAMAB	PC	Standardized Difference	Total
Refractory status				
N	116	546	0.1882	662
<= Double refractory	52 (45.2%)	275 (50.4%)		328 (49.5%)
Triple/Quad refractory	61 (52.7%)	246 (45.1%)		307 (46.4%)
(At least) Penta refractory	2 (2.1%)	25 (4.5%)		27 (4.1%)
N prior lines				
N	116	546	-0.0091	662
<= 4	96 (83.1%)	452 (82.8%)		548 (82.9%)
5+	20 (16.9%)	94 (17.2%)		114 (17.1%)
Months since diagnosis				
N	116	546	0.1090	662
1-47	42 (36.2%)	227 (41.6%)		269 (40.6%)
48+	74 (63.8%)	319 (58.4%)		393 (59.4%)
Age				
N	116	546	-0.2171	662
<65	39 (33.6%)	130 (23.9%)		169 (25.6%)
>= 65	77 (66.4%)	416 (76.1%)		493 (74.4%)
ECOG				
N	116	546	-0.0245	662
0	25 (21.6%)	113 (20.6%)		138 (20.8%)
1	91 (78.4%)	433 (79.4%)		524 (79.2%)

Source: Janssen Data on File

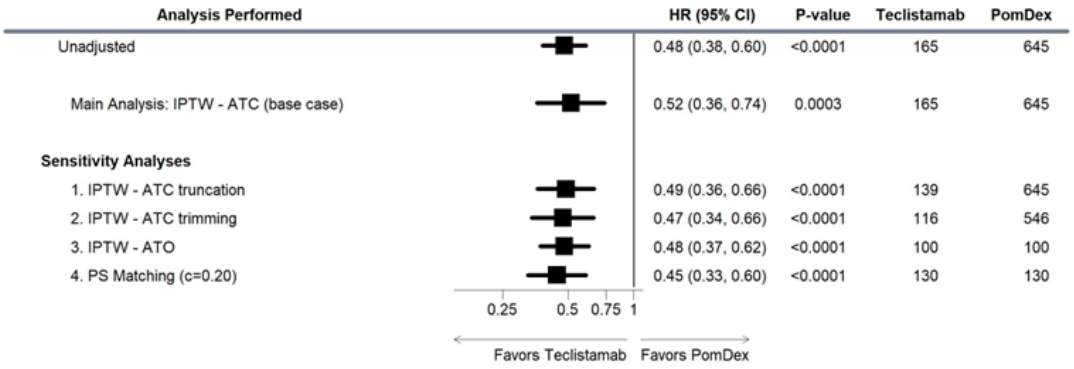
Figure 6. Distribution of PSs after ATC with trimming for patients in MajesTEC-1 and the PomDex cohort



Source: Janssen Data on File

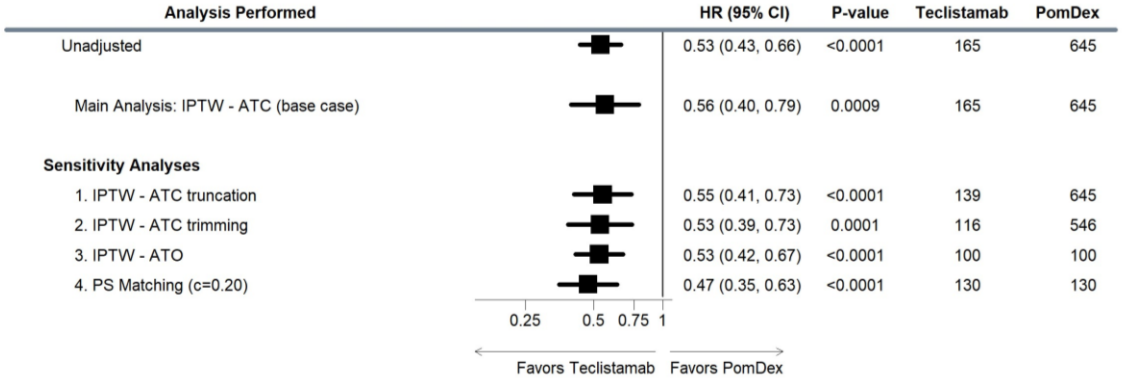
Results

Figure 7. Base case and sensitivity analyses (including ATC trimming and truncation) for OS



Source: Janssen Data on File

Figure 8 Base case and sensitivity analyses (including ATC trimming and truncation) for TTNT



Source: Janssen Data on File

Appendix 4: PS matching and ATO: methodology, SMDs and distribution of propensity scores

Methodology

PS matching:

- We conducted a 1:1 optimal matching based on the logit of the propensity scores. We used 0.2 of the pooled standard deviation of the logit of the propensity score as caliper width (Austin 2011)[3].

- Optimal matching selects all control units that match each treated unit by minimizing the total absolute difference in propensity score across all matches. Optimal matching selects all matches simultaneously and without replacement.

ATO:

- While PS matching only includes a limited subset of patients with similar PS, the ATO uses data from all patients. More specifically, ATO smoothly up-weights patients with substantial probability of receiving either treatment or down-weighs the patients with extreme PS (Fan *et al* 2019)[4]. The overlap weight is defined as 1−PS for teclistamab patients and equal to PS for UKk patients.

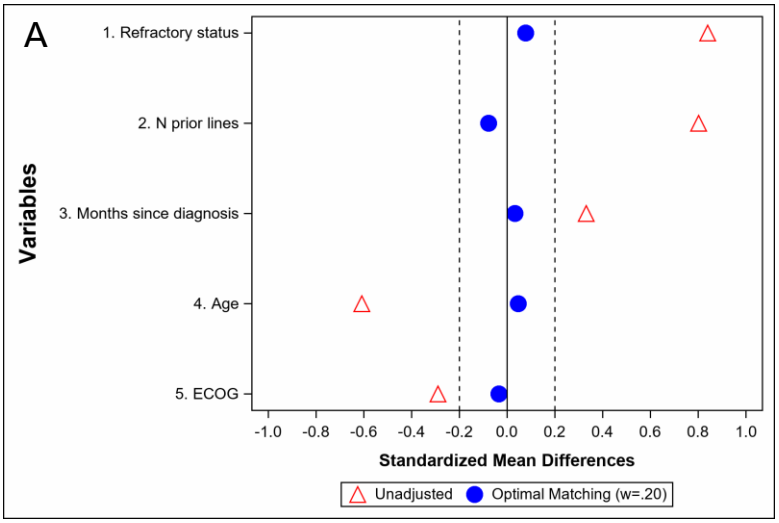
- However, since ATO focuses on patients with the most overlap in their observed characteristics, it provides estimates of the average treatment effect in the overlap population, and therefore it was not considered as base case where the aim was to reflect the UK population.

[3]Austin, Peter C. "Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies." *Pharmaceutical statistics* 10.2 (2011): 150-161.

[4] Li, Fan, Laine E. Thomas, and Fan Li. "Addressing extreme propensity scores via the overlap weights." *American journal of epidemiology* 188.1 (2019): 250-257.

SMDs and distribution of propensity scores

Figure 9A and B SMDs between the MajesTEC-1 and PomDex cohorts after PS matching (c=20)

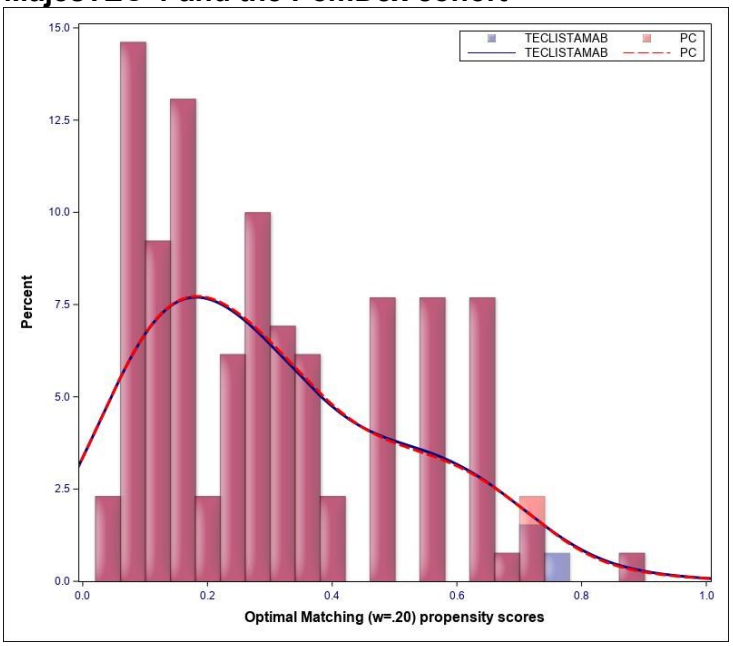


B

	TECLISTAMAB	PC	Standardized Difference	Total
Refractory status				
N	130	130	0.0775	260
<= Double refractory	37 (28.5%)	40 (30.8%)		77 (29.6%)
Triple/Quad refractory	75 (57.7%)	75 (57.7%)		150 (57.7%)
(At least) Penta refractory	18 (13.8%)	15 (11.5%)		33 (12.7%)
N prior lines				
N	130	130	-0.0776	260
<= 4	76 (58.5%)	71 (54.6%)		147 (56.5%)
5+	54 (41.5%)	59 (45.4%)		113 (43.5%)
Months since diagnosis				
N	130	130	0.0336	260
1-47	38 (29.2%)	40 (30.8%)		78 (30%)
48+	92 (70.8%)	90 (69.2%)		182 (70%)
Age				
N	130	130	0.0463	260
<65	68 (52.3%)	71 (54.6%)		139 (53.5%)
>= 65	62 (47.7%)	59 (45.4%)		121 (46.5%)
ECOG				
N	130	130	-0.0338	260
0	39 (30%)	37 (28.5%)		76 (29.2%)
1	91 (70%)	93 (71.5%)		184 (70.8%)

Source: Janssen Data on File

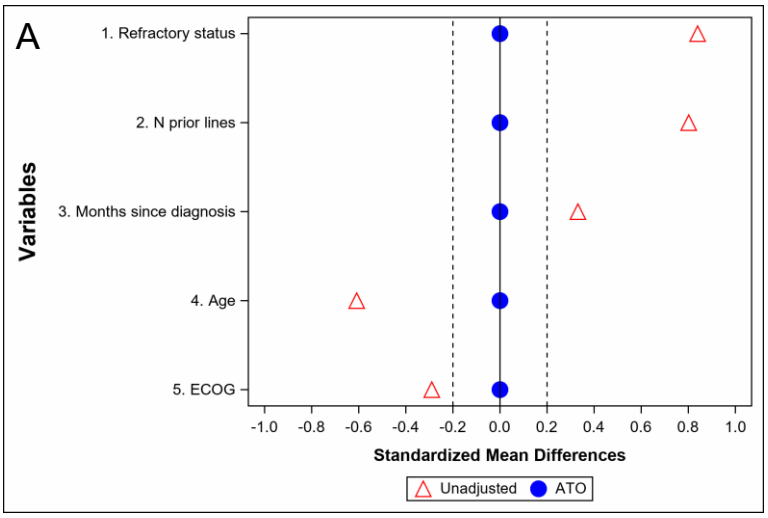
Figure 10 Distribution of PSs after PS matching (c=20) for patients in MajesTEC-1 and the PomDex cohort



Source: Janssen Data on File

Figure 11A and B. SMDs between the MajesTEC-1 and PomDex cohorts after ATO

A

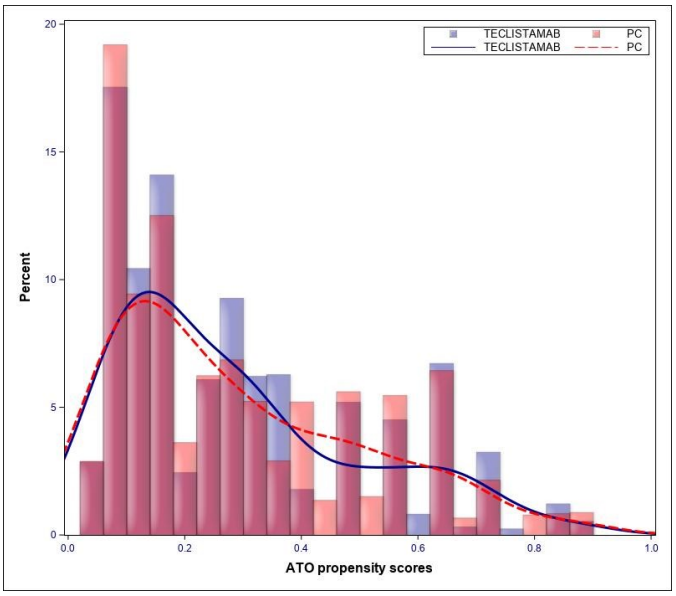


B

	TECLISTAMAB	PC	Standardized Difference	Total
Refractory status				
N	100	100	0.0000	200
<= Double refractory	31 (30.6%)	31 (30.6%)		61 (30.6%)
Triple/Quad refractory	54 (54.1%)	54 (54.1%)		108 (54.1%)
(At least) Penta refractory	15 (15.3%)	15 (15.3%)		31 (15.3%)
N prior lines				
N	100	100	0.0000	200
<= 4	61 (61.1%)	61 (61.1%)		122 (61.1%)
5+	39 (38.9%)	39 (38.9%)		78 (38.9%)
Months since diagnosis				
N	100	100	0.0000	200
1-47	31 (31%)	31 (31%)		62 (31%)
48+	69 (69%)	69 (69%)		138 (69%)
Age				
N	100	100	-0.0000	200
<65	46 (46.1%)	46 (46.1%)		92 (46.1%)
>= 65	54 (53.9%)	54 (53.9%)		108 (53.9%)
ECOG				
N	100	100	-0.0000	200
0	30 (29.9%)	30 (29.9%)		60 (29.9%)
1	70 (70.1%)	70 (70.1%)		140 (70.1%)

Source: Janssen Data on File

Figure 12. Distribution of PSs after ATO for patients in MajesTEC-1 and the PomDex cohort



Source: Janssen Data on File

Appendix 5: Teclistamab KM curves and extrapolations for EAG Scenario S6

Figure 13. Teclistamab KM curves and extrapolations for EAG Scenario S6 (pessimistic scenario): OS, PFS and TTD