Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

Part 1 for public and presentation – redacted

Technology appraisal committee C [4 June 2024]

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Company: Johnson & Johnson Innovative Medicine

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

- ✓ **Background**
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Equality, managed access and severity
- ❑ Summary

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Background on multiple myeloma

Multiple myeloma is a rare, incurable type of haematological cancer

Causes

- Multiple myeloma is a malignancy of plasma cells in the bone marrow

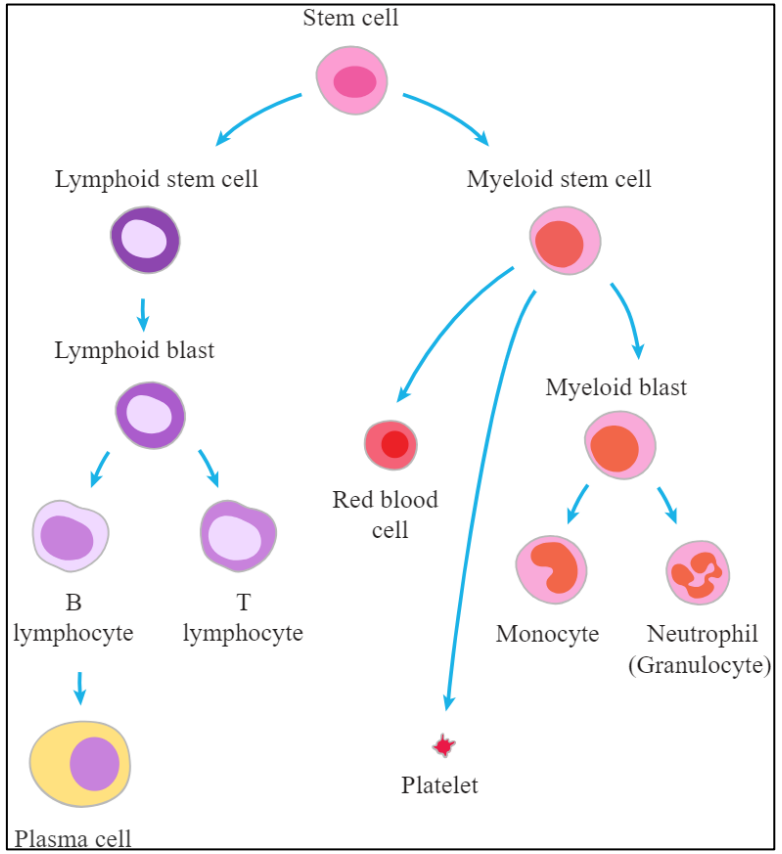
Epidemiology

- Accounts for 2% of all new cancer cases and is more common in men than women
- Median age at diagnosis is around 74 years
- Approximately 6,000 new cases of multiple myeloma per year in UK (incidence rate: 9.7/100,000)

Symptoms and prognosis

- Symptoms and complications include bone pain and fractures; tiredness, weakness and shortness of breath caused by anaemia; high levels of calcium in the blood (hypercalcaemia); kidney problems and repeated infections
- 5-year survival rate for people who are newly diagnosed is around 55%
- Multiple myeloma is considered incurable; all people will eventually progress or relapse

Figure 5: Blood cells and Myeloma



Source: Cancer Research UK

Patient and carer perspectives

Myeloma has significant impact on quality of life of patients and carers

Submissions from Myeloma UK and Blood Cancer UK:

- Complications of myeloma can be significant, debilitating and painful, and have a substantial impact on quality of life, including physical, social and work life
- The relapsing-remitting nature of myeloma has a huge psychological impact, as people are aware that treatment options and life expectancy reduce with each relapse
- Caring for someone with myeloma is extremely physically and emotionally challenging – many carers mention changes in their social life, relationships, income, and wider family dynamics
- There is an unmet need for innovative treatments which deliver deep, durable responses
- Teclistamab has the potential to overcome treatment resistance and fulfil this unmet meet
- Weekly and bi-weekly subcutaneous injection without combination with steroids is a distinct advantage of this treatment

"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."

"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

Clinical perspectives

Teclistamab provides a new treatment option for difficult to treat myeloma

Joint submission from UK Myeloma Society, Royal College of Physicians and Royal College of Pathologists and submission from Royal College of Pathologists

- Myeloma is incurable – the aim of treatment is to prolong survival, delay progression, and maintain or improve quality of life
- Current NHS treatments after 3 prior therapies include pomalidomide / bortezomib / panobinostat with dexamethasone
- Teclistamab will provide a new treatment modality for patients with difficult to treat disease
- Currently available drugs induce a response in only a third of patients. Teclistamab trial shows up to 63% response with meaningful improvement in overall survival
- Requires inpatient treatment for the first 2 to 3 doses – monitoring for cytokine release syndrome and severe infections is required

"Teclistamab provides deep and durable responses for patients who currently have limited treatment options available. This translates to improved prognosis and quality of life"

"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"

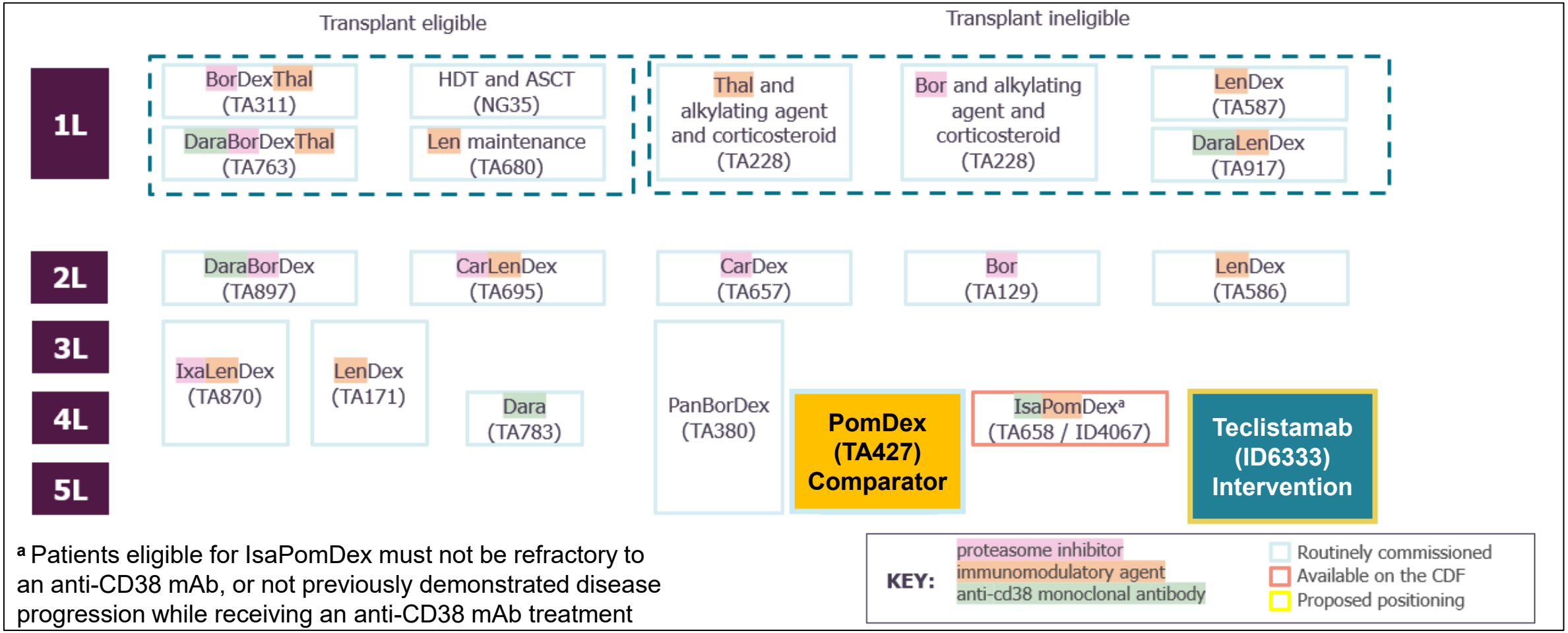
Teclistamab (Tecvayli, Johnson & Johnson Innovative Medicine)

Marketing authorisation	MHRA approval granted on 09 November 2022 for use *"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."*
Mechanism of action	Bispecific monoclonal antibody that targets the CD3 receptors expressed on the surface of T cells, and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw CD3+ T cells in close proximity to BCMA+ cells, resulting in T cell activation and subsequent lysis and death of BCMA+ cells
Administration	Subcutaneous injection • 1.5mg/kg once weekly, 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 for at least 6 months may reduce the dose frequency to 1.5mg/kg every two weeks
Price	• The list price for teclistamab is £775.14 (10mg vial) and £3,952.78 (90mg vial) • Company has a confidential PAS discount in place

MHRA: Medicines & Healthcare Products Regulatory Agency; PAS: Patient access scheme

Multiple myeloma (MM) treatment pathway and proposed positioning of teclistamab

Figure 1: 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

Source: Company submission, Figure 6

See appendix: Decision problem

ASCT: Autologous stem cell transplantation; Bor: Bortezomib; Car: Carfilzomib; CDF: Cancer Drugs Fund; Dara: Daratumumab; Dex: Dexamethasone; Isa: Isatuximab; Ixa: Ixazomib; Len: Lenalidomide; PAN: Panobinostat; POM: Pomalidomide; TA: Technology appraisal; Tec: Teclistamab; Thal: Thalidomide.

Key issues

Issue	Resolved?	ICER impact*
Clinical effectiveness		
Clinical effectiveness evidence for teclistamab and pomalidomide plus dexamethasone	No – for discussion	Unknown
Indirect treatment comparison methods	No – for discussion	Unknown
Cost-effectiveness		
Company's approach to generating overall survival and progression free survival for pomalidomide plus dexamethasone	No – for discussion	Small
Company's method to generate time to treatment discontinuation for teclistamab and pomalidomide plus dexamethasone	No – for discussion	Small
Switching from a teclistamab Q1W to a Q2W regimen	No – for discussion	Small
Utility values	No – for discussion	Small
Costs of immunoglobulin use	No – for discussion	Unknown
Drug wastage	No – for discussion	Unknown

* Both the company and EAG applied a severity weight of 1.2 to the incremental QALYs

ICER: Incremental cost effectiveness ratio; Q1W: Once weekly; Q2W: Every two weeks

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Key results: MajesTEC-1 and UK RW TCE RRMM

MajesTEC-1 and UK RW TCE RRMM study results

	MajesTEC-1: all treated analysis set (N=165)	UK RW TCE RRMM: PomDex ECOG PS 0/1 (N=645)
Median follow-up, months	30.4[a]	26.0
ORR (95% CI)	63.0 [redacted]	NR
Median PFS, months (95% CI)	11.4 (8.8 to 16.4)	NR
Median TTNT, months (95% CI)*	12.6 (8.7 to 17.4)	7.03 (6.54 to 7.81)
Median OS, months (95% CI)	22.2 (15.1 to 29.9)	9.78 (8.64 to 10.82)

Source: EAG report, Table 10

[a] Median OS follow-up; median PFS follow-up was [redacted]

* In the absence of PFS data for PomDex from UK RW TCE RRMM study company used TTNT as proxy for PFS. Clinical advice to the EAG agreed that TTNT is an appropriate proxy to PFS

See appendix: MajesTEC-1 study design, Key clinical effectiveness evidence: overview, Baseline characteristics: MajesTEC-1 and UK RW TCE RRMM, Teclistamab real world evidence, Adverse events: MajesTEC-1

CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TCE RRMM: Triple-class exposed relapsed or refractory multiple myeloma; TTNT: Time to next treatment

Unknown impact ?

Key issue: Clinical effectiveness evidence for teclistamab and PomDex

Company

- Clinical effectiveness evidence for teclistamab based on MajesTEC-1, a single arm, phase I/II trial
  - Company also reported clinical effectiveness evidence results from two real-world, retrospective studies, Dima et al. 2023 and Riedhammer et al. 2024) ➔ **Not used in cost-effectiveness analysis**
- Clinical effectiveness evidence for PomDex based on UK RW TCE RRMM, a retrospective registry study

EAG comments

- There is limited clinical effectiveness data available to support the use of teclistamab or PomDex
  - No direct comparative evidence available for teclistamab versus any active comparator
  - In the absence of clinical trial evidence for PomDex, only real-world registry data are available

See Key issues and questions for committee
See appendix: MajesTEC-1 study design, Key clinical effectiveness evidence: overview, Baseline characteristics: MajesTEC-1 and UK RW TCE RRMM, Teclistamab real world evidence

What impact does the uncertainty in the clinical effectiveness evidence for teclistamab and PomDex have on the decision making?

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PomDex: Pomalidomide plus dexamethasone

Unknown impact ?

Key issue: ITC methods

Company

- Adjusted ITCs were used to inform comparative effectiveness of teclistamab versus PomDex using individual patient data from MajesTEC-1 and UK RW TCE RRMM in the absence of direct comparative evidence ➔ Hazard ratios reported for OS and TTNT (TTNT used as proxy for PFS)
- Adjustments for confounding variables were made using the inverse probability of treatment weighting method using propensity scores to derive weights to balance baseline characteristics of patients in the teclistamab arm and the PomDex arm ➔ Explored other adjustment methods, including multivariable regression and propensity score matching in sensitivity analyses
- Adjustment for five variables (refractory status, number of prior lines of treatment, ECOG PS, age and months since diagnosis) was the most appropriate approach since overlap between the populations improved compared with adjusting for six variables
    - ASCT was identified as a covariate, but was removed from the weighting process as no statistically significant differences in OS or TTNT was found between people with or without prior ASCT
- 5-variable adjustment approach generated more conservative efficacy results for teclistamab than the 6-variable adjustment approach

See Key issues and questions for committee
See appendix: ITC methods - identification of co-variates

ECOG PS: Eastern Cooperative Oncology Group performance status; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTNT: Time to next treatment

ITC method – assessment of overlap

Before adjustment all 6 co-variates had standardised mean differences (SMD) above threshold of 0.2

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

		Before adjustment			After adjustment		
		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 lines of treatment, 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 PS, 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 ASCT, 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)	

Source: Company submission, Table 27

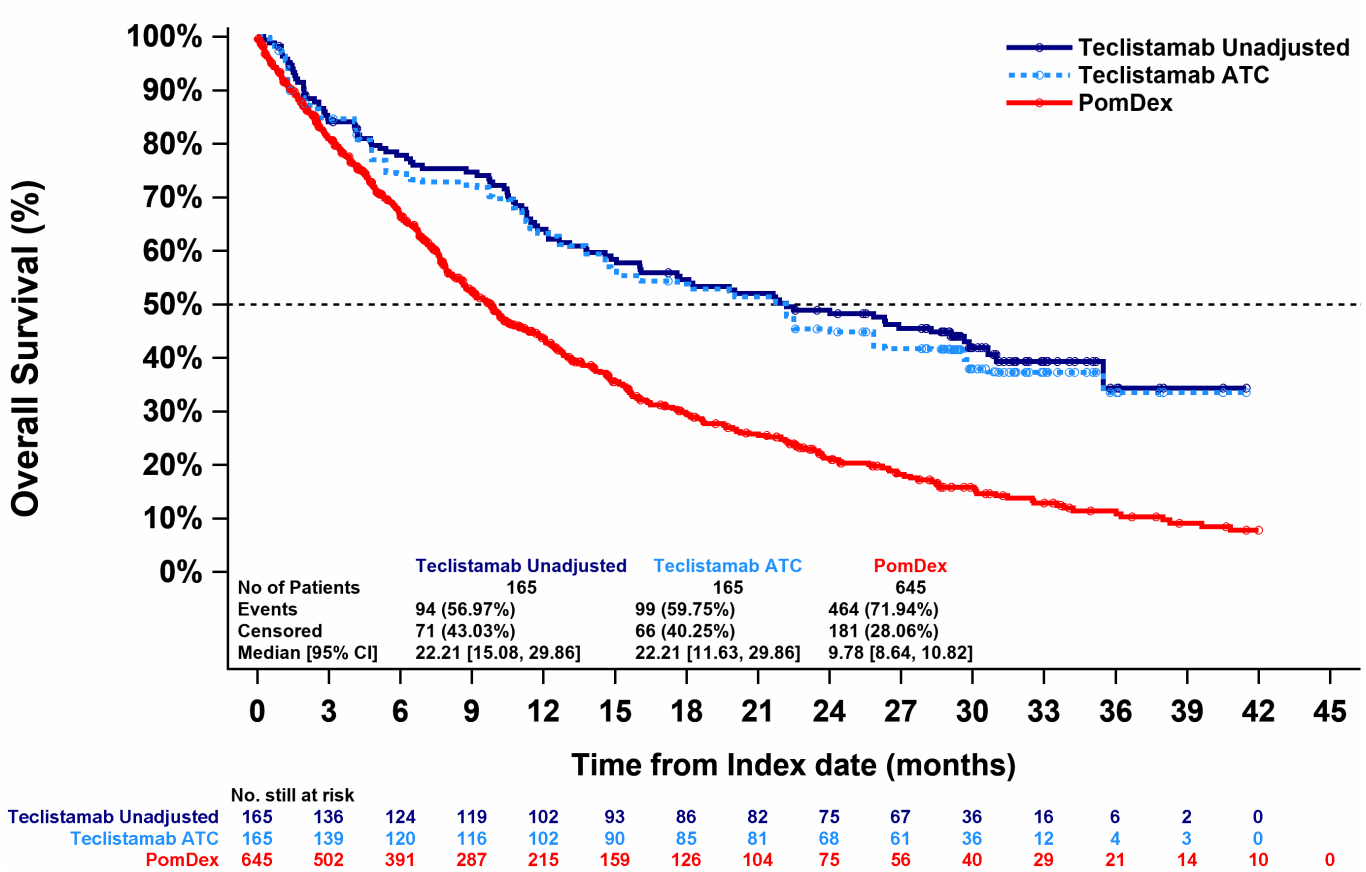
See appendix: ITC methods - identification of co-variates

ASCT: Allogenic stem cell transplant; ECOG PS: Eastern Cooperative Oncology Group performance status; ITC: Indirect treatment comparison; PomDex: Pomalidomide plus dexamethasone; SMD: standardised mean differences

ITC results – OS

Adjusted indirect treatment comparisons were used to compare the treatment effect of teclistamab from MajesTEC-1 to PomDex from UK RW TCE RRMM

Figure 2: Kaplan–Meier (KM) of OS MajesTEC-1 versus UK RW TCE RRMM



	Teclistamab ESS=[redacted]	PomDex N=645
Median (months)	22.21	9.78
Hazard ratio (HR [95% CI])	0.52 (0.36 to 0.74)	

Source: EAG report, Table 15

Source: Company submission, Figure 31

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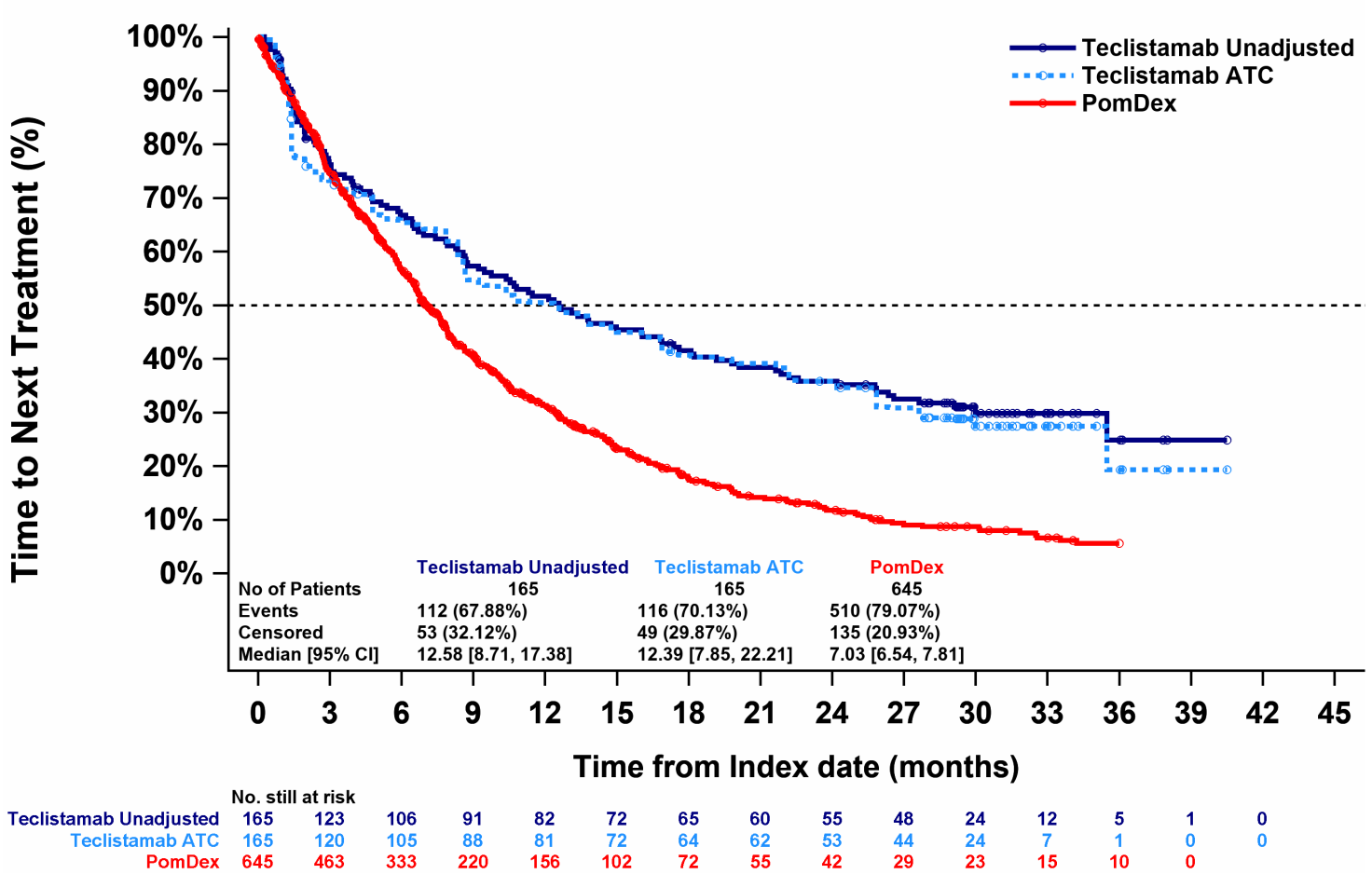
CI: Confidence interval; ESS: effective sample size; ITC: Indirect treatment comparison; OS: Overall survival; PomDex: Pomalidomide plus dexamethasone

ITC results – TTNT

Figure 3: Kaplan–Meier of TTNT MajesTEC-1 versus UK RW TCE RRMM



	Teclistamab ESS=[redacted]	PomDex N=645
Median (months	12.39	7.03
HR (95% CI)	0.56 (0.40 to 0.79)	

Source: EAG report, Table 15

Source: Company submission, Figure 32

CI: Confidence interval; ESS: effective sample size; HR: Hazard ratio; ITC: Indirect treatment comparison; PomDex: Pomalidomide plus dexamethasone; TTNT: Time to next treatment

Unknown impact ?

Key issue: ITC methods

EAG comments

- IPTW method may be unstable, and the estimated treatment effects may be biased
  - SMDs were greater than 0.25 for all six co-variates initially identified for overlap between populations prior to adjustment ➔ Predicted propensity scores may be close to zero, leading to excessively large weights
  - Did not present adjusted SMDs due to concerns regarding the appropriateness of the IPTW method
- In presence of problems with overlap, company's base case analyses did not employ DSU guidance to perform trimming of the sample, or matching, to improve overlap
- Four priority prognostic factors (cytogenetic profile, ISS stage, time to progress on last regimen, extramedullary plasmacytoma) not adjusted
  - Clinical advice to the EAG is that cytogenetic profile is the most important factor
- Violation of proportional hazard assumption introduces further uncertainty regarding the accuracy of reported HRs
- Average treatment effect for the control weighting in the base case analysis was appropriate

See Key issues and questions for committee

Do the adjusted ITC results provide a good reflection of relative efficacy of teclistamab versus PomDex?

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DSU: Decision support unit; HRs: Hazard ratios; IPTW: Inverse probability of treatment weighting; ISS: International staging system; ITC: Indirect treatment comparison; SMDs: Standardised mean differences; TTNT: Time to next treatment

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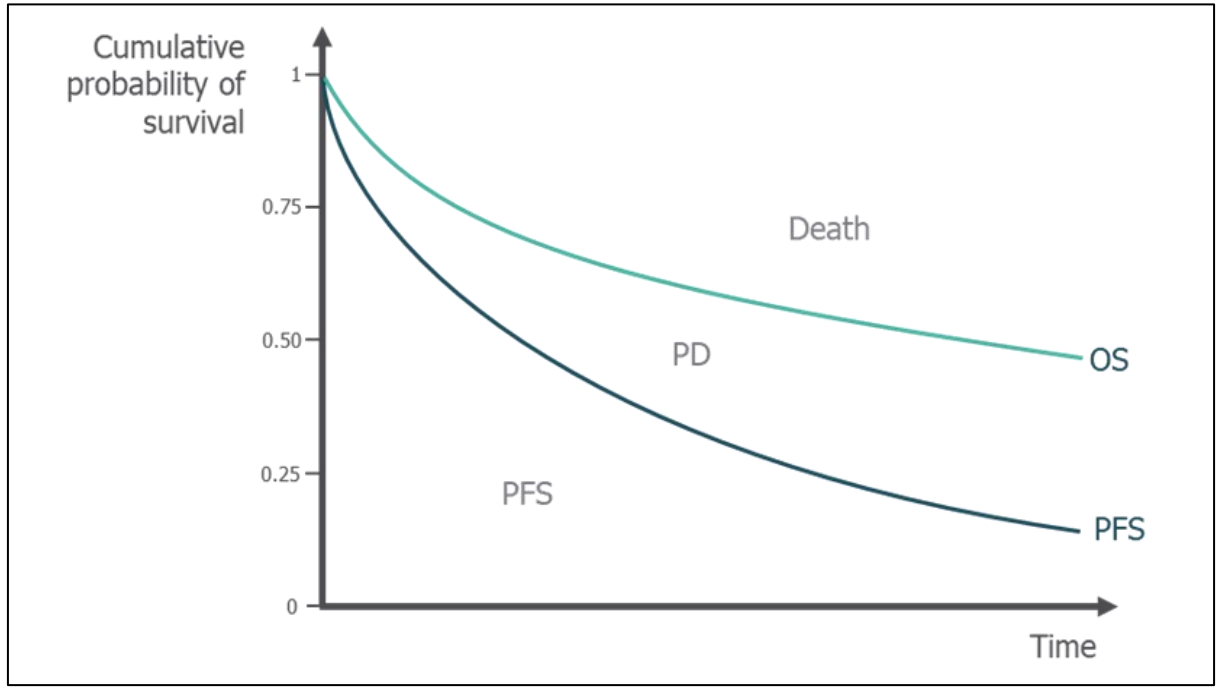
Company's model overview

- Partitioned survival cohort simulation model
- Life-time horizon of 40 years using 1-week cycles
- State occupancy informed by OS and PFS from MajesTEC-1 trial for teclistamab arm and from UK RW TCE for PomDex arm

Figure 4: Model structure



Source: EAG report, Figure 2

Teclistamab affects QALYs by:

- Increasing survival
- Having a different adverse event profile

Teclistamab affects costs by:

- Having different acquisition and administration costs
- Increasing health care resource use by increasing survival
- Reducing subsequent treatment costs
- Increasing adverse event costs

Assumptions with greatest effect on cost effectiveness results:

- Progression free and progressed disease health state utility values for teclistamab arm and PomDex arm derived from MajesTEC-1 trial data

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OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; QALY: Quality-adjusted life year

Small impact

Key issue: Company's approach to generating OS, PFS and TTD (1)

Company

OS and PFS:

- Parametric distributions fitted to MajestTEC-1 (teclistamab arm) and UK RW TCE RRMM (PomDex arm) K-M data were used to generate OS and PFS estimates – TTNT used as proxy for PFS
- Best fitting curve selected based on statistical fit (AIC and BIC scores) and validated using clinical advice
- Selected OS and PFS curves were attenuated so that OS and PFS estimates aligned with midpoint of clinical experts' estimates at 10- and 15-years ➔ In company's base case, attenuation of selected OS and PFS curves is applied to teclistamab arm only

TTD:

- Parametric distributions fitted to MajestTEC-1 K-M data were used to generate TTD estimates for teclistamab arm
- In the absence of PomDex TTD data, TTD estimates are generated by applying teclistamab median TTD: teclistamab median PFS ratio to PomDex TTNT (a proxy for PFS) K-M data
- Curve selection based on distribution which generated TTD estimates at 10- and 15-years that were close to clinician estimates but were a poorer statistical fit

See Key issues and questions for committee
See appendix slide 44-49: Long term OS, PFS and TTD estimates

AIC: Akaike information criterion; BIC: Bayesian information criterion; KM: Kaplan-Meier; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTD: Time to treatment discontinuation; TTNT: Time to next treatment

Clinical expert validation of long-term survival outcomes

In an advisory board, company asked 3 clinicians to provide estimates of the most likely PFS/OS/TTD for teclistamab and PomDex at 5-, 10- and 15-years, as well as the lower plausible limit and upper plausible limit of survival at these time points

Clinical expert estimates of OS, PFS and TTD for teclistamab at 5, 10 and 15 years

	Teclistamab arm			PomDex arm		
	5 years	10 years	15 years	5 years	10 years	15 years
OS						
Lowest plausible limit	8%	2%	0%	2%	0%	0%
Most likely value (range)	**12–30%**	**5–15%**	**1–5%**	**5-15%**	**0-5%**	**0-1%**
Upper plausible value	40%	25%	10%	25%	8%	5%
PFS						
Lowest plausible limit	3%	0%	0%	0%	0%	0%
Most likely value (range)	**7–20%**	**2–8%**	**0–2%**	**2-10%**	**0-5%**	**0-0%**
Upper plausible value	30%	15%	5%	20%	10%	5%
TTD						
Lowest plausible limit	0%	0%	0%	0%	0%	0%
Most likely value (range)	**4-20%**	**1-5%**	**0-2%**	**0-8%**	**0-3%**	**0-0%**
Upper plausible value	30%	10%	5%	15%	8%	2%

Source: Company submission, Janssen Data on File. UK Advisory Board Meeting Report (2023); Tables 2-7

Most optimistic for teclistamab

Most pessimistic for teclistamab

See appendix slide 44-49: Long term OS, PFS and TTD estimates

OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTD: Time to treatment discontinuation

Small impact

Key issue: Company's approach to generating OS, PFS and TTD (2)

EAG comments

- Consider that the company approach to curve selection for OS, PFS and TTD should have been consistent between arms, i.e. selection of relevant curve that was the best fit based on AIC scores and attenuated to generate estimates that aligned with midpoint of clinician 10- and 15-year likely values
- Clinician estimates are based on only 3 clinical experts and does not use the Delphi panel technique
  - Only provides a plausible estimate and not exact values ➔ Upper and lower bounds of clinician estimates are wider than the range for the clinicians most likely values
- Revised the model using attenuated curves for OS, PFS and TTD estimates for teclistamab arm and PomDex arm so they aligned with midpoint of clinicians 10- and 15-year likely values

See Key issues and questions for committee
See appendix slide 44-49: Long term OS, PFS and TTD estimates

AIC: Akaike information criterion; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTD: Time to treatment discontinuation

Small impact

Key issue: Company's approach to generating OS, PFS and TTD (3)

See Key issues and questions for committee
See appendix slide 44-49: Long term OS, PFS and TTD estimates

	Company approach				EAG comments
	Teclistamab		PomDex		
	Curve	Attenuated	Curve	Attenuated	
OS	Lognormal	Yes	Gompertz	No	• Company selected gamma curve for teclistamab TTD (poorer statistical fit but TTD estimates close to clinician most likely values. • EAG prefers lognormal curve (best statistical fit) • Company attenuates only OS and PFS for teclistamab arm only. EAG attenuates OS, PFS and TTD for both teclistamab arm and PomDex arm in its preferred analysis • Considers impact of curve selection for OS, PFS and TTD is small once attenuation is applied
PFS	Lognormal	Yes	Gompertz	No	
TTD	Gamma	No	Gompertz (PomDex PFS)	No	

- Should the selected curves for OS, PFS and TTD be attenuated consistently for both teclistamab arm and PomDex arm, to align with midpoint of clinician 10- and 15-year likely values?
- Should the Gamma or lognormal distribution be used to estimate TTD for teclistamab arm?

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OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTD: Time to treatment discontinuation

Small impact

Key issue: Switching teclistamab Q1W to Q2W regimen

Company

- Proportion of patients who received teclistamab and had a complete response (CR) or better for at least 6 months switched from Q1W to Q2W regimen determined by fitting parametric distributions to MajesTEC-1 trial dose switching K-M data ➔ Model patients switching to the Q2W regimen from [redacted] weeks

EAG comments

- Company's approach to switching to Q2W at [redacted] weeks is implausible ➔ Teclistamab SmPC states that a Q2W regimen is only permitted for patients who have experienced at least 6 months of CR and the MajesTEC-1 trial mean time to CR was [redacted] months
- The EAG revised the company model so that switching to the Q2W regimen started at week 52 (median time to CR + 6 months) ➔ MajesTEC-1 trial data shows that at 52 weeks only [redacted] of patients still receiving teclistamab had switched to the Q2W regimen
- From week 53, treatment switching reflects the proportion of MajesTEC-1 trial patients who switched to Q2W at different time points
- EAG revision increases the ICER

See Key issues and questions for committee

Is the EAG's approach to model patients switching from teclistamab Q1W to Q2W regimen at 52 weeks appropriate for decision making?

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ICER: Incremental cost effectiveness ratio; KM: Kaplan-Meier; Q1W: Once weekly; Q2W: Every two weeks; SmPC: Summary of product characteristics

Small impact

Key issue: Utility values

Company

- Utility values for teclistamab derived from health-related quality of life (HRQoL) data collected from MajesTEC-1 trial EQ-5D-5L data mapped to EQ-5D-3L using the algorithm developed by the DSU
- Utility values for PomDex based on values accepted by NICE in TA510 and TA783

Teclistamab				PomDex		
Health state	**Time (number of 28-day cycles)**	**Utility**	**Source**	**Health state**	**Utility**	**Source**
Progression-free	0	[redacted]	MajesTEC-1 (August 2023 DCO, Company submission model with the lowest AIC)	**Progression-free**	**0.61**	MM-003 trial (TA510/TA783)
	2	[redacted]				
	4	[redacted]				
	6	[redacted]				
	8	[redacted]				
	10	[redacted]				
	12	[redacted]				
	14	[redacted]				
	16	[redacted]				
	18	[redacted]				
	20	[redacted]				
	22	[redacted]				
	24 or more	[redacted]				
Progressed disease	All model cycles	[redacted]		**Progressed disease**	**0.57**	

Source: Company submission, Tables 52-54

See Key issues and questions for committee

AIC; Akaike information criterion; DSU: Decision support unit; PomDex: Pomalidomide plus dexamethasone; TA: Technology appraisal

Small impact

Key issue: Utility values

EAG prefers same health state utility values for teclistamab and PomDex arm based on MajesTEC-1 data

EAG comments

- Revised the company model by using utility values generated from MajesTEC-1 trial data to reflect HRQoL for patients treated with both teclistamab and PomDex ➔ Based on clinical advice to the company that it would be appropriate to use utility values derived from MajesTEC-1 trial data to reflect HRQoL for patients treated with PomDex
- The company has not presented any clinical evidence to support using lower baseline progression-free health state utility value for PomDex arm compared with teclistamab arm
- In the company's model, utility values for the teclistamab arm increase over time in the progression-free health state but remain same for the PomDex arm. This is contrary to clinical advice to the company that it is appropriate to model improving HRQoL over time for the progression free health state regardless of treatment
- EAG revision increases the ICER

See Key issues and questions for committee

Which approach to inform utility values for PomDex arm is more appropriate?

- Values accepted by NICE in TA510 and TA783 **– Company base case**
- MajesTEC-1 EQ-5D data **– EAG base case**

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HRQoL: Health-related quality of life; ICER: Incremental cost effectiveness ratio; PomDex: Pomalidomide plus dexamethasone; TA: Technology appraisal

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- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ✓ **Base case assumptions and cost-effectiveness results**
- ❑ Other considerations: Equality, innovation, managed access and severity
- ❑ Summary

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Differences between company and EAG base case assumptions

Assumption	Company base case	EAG base case
OS, PFS extrapolation	Attenuate OS and PFS for teclistamab arm only to mid-point of clinical expert likely values	Attenuate OS and PFS for both teclistamab arm and PomDex arm to mid-point of clinical expert likely values
TTD extrapolation	• Teclistamab: Gamma distribution • PomDex: applied teclistamab median TTD: PFS ratio to PomDex TTNT K-M data	• Teclistamab: Lognormal distribution • Attenuate teclistamab and PomDex curves to mid-point of clinical expert likely values
Switching teclistamab Q1W to Q2W regimen	At [redacted] weeks	At 52 weeks followed by MajesTEC-1 data
Utility values	• Teclistamab: MajesTEC-1 • PomDex: TA510 and TA783	• Teclistamab: MajesTEC-1 • PomDex: MajesTEC-1
Teclistamab skipped doses	[redacted] applied only to the maintenance doses of teclistamab	[redacted] applied only to maintenance doses of teclistamab (MajesTEC-1)

See appendix: Teclistamab skipped doses

OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; Q1W: Once weekly; Q2W: Every two weeks; TA: Technology appraisal; TTD: Time to treatment discontinuation

Cost-effectiveness results*

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- When comparator PAS discounts are included, the company base case is within the range normally considered a cost-effective use of NHS resources
- The EAG base case is also within this range
- Scenarios presented in Part 2 will include alternative OS, PFS and TTD modelling approaches

* Both the company and EAG applied a severity weight of 1.2 to the ICER

ICER: Incremental cost effectiveness ratio; OS: Overall survival; PAS: Patient access scheme; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Other considerations: Equality, managed access and severity**
- ❑ Summary

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Unknown impact ?

Other considerations (1) - costs of immunoglobulin use

Company

- Immunoglobulin use considered in previous NICE appraisals committee meetings for a similar indication
- Used MajesTEC-1 data to inform immunoglobulin dosing in base case ➔ Provided scenarios varying the duration of intravenous immunoglobulin (IVIG) use (6, 9 and 10 doses) and proportion of patients receiving IVIG (39% [SmPC] and [redacted] [MajestEC-1])
- Unreasonable to adjust costs or outcomes of immunoglobulin use independently
- Final scope does not define intervention as teclistamab in combination with IVIG

Immunoglobulin dosing regimen: Company base case

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

Source: Company submission, Table 62

EAG comments

- Appropriate to understand how changes in IVIG use may impact the cost of treatment with teclistamab
- Agree with the company that, without understanding the impact of IVIG on patient outcomes, the real impact of increased IVIG use on the cost effectiveness of teclistamab is unclear

NHS England comments

- Clinical advice suggests that people who respond to teclistamab will require secondary prophylaxis with immunoglobulin for substantial periods of time ➔ Scenario analyses should include at least 50% of the trial population having at least 6 and 10 doses of immunoglobulin

See Key issues and questions for committee

How many doses and what proportion of patients should receive IVIG in the economic model?

IV: Intravenous; SC: Subcutaneous

Unknown impact ?

Other considerations (2) – drug wastage

Company

- Assumes teclistamab drug wastage will be limited (15%) ➔ Vial sharing is encouraged by NHS England (TA862, TA819, TA704) and drug wastage assumptions in previous appraisals were accepted (TA658)
- In an early access programme for teclistamab the volume of drug wastage was estimated to be [redacted] on maintenance doses ([redacted] including step-up doses)
  - Vial sharing was not permitted, implying that drug wastage in the early access programme would be higher than it would be in standard UK clinical practice, where vial sharing would be encouraged

EAG comments

- Given the evidence presented by the company, drug wastage is likely to be closer to 15% than 25%.

NHS England comments

- Drug wastage of teclistamab varies according to the weight of patients
- Teclistamab vial sharing is unlikely in clinical practice
- Calculated 28.8% wastage of teclistamab if no vial sharing occurs ➔ Should be used in the model
- Alternatively, costs for each patient in the model should be dependent on the number of whole vials being used rather than on a teclistamab cost per mg basis

See Key issues and questions for committee

What proportion of teclistamab wastage should be used in the economic model?

NICE

Other considerations (3)

Equality considerations

- Patient carer submission: **Blood Cancer UK**
  - Teclistamab may need to be delivered at more well-equipped centres with specifically trained healthcare professionals ➔ This poses challenges for patients who live further from centres and cannot afford, for financial or logistical reasons, to travel longer distances
  - Issues around capacity for day units and inpatient access may also cause unequal access to this treatment

Potential for managed access

- Managed access [redacted] by the company
  - Company submission is based on the [redacted], and [redacted] data are expected to become available in this patient population to inform decision making

Severity weighting

- Company and EAG agree 1.2 QALY weighting is appropriate

See appendix: QALY weightings for severity, Managed access

Are there any equality issues?

QALY: Quality-adjusted life year

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Equality, managed access and severity
- ✓ **Summary**

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Key issues and questions for committee

Clinical effectiveness issues

Clinical effectiveness evidence for teclistamab and PomDex

- What impact does the uncertainty in the clinical effectiveness evidence for teclistamab and PomDex have on the decision making?

ITC methods

- Do the adjusted ITC results provide a good reflection of relative efficacy of teclistamab versus PomDex?

Cost-effectiveness issues

Company's approach to generating OS, PFS and TTD

- Should the selected curves for OS, PFS and TTD be attenuated consistently for both teclistamab arm and PomDex arm, to align with midpoint of clinician 10- and 15-year likely values?
- Should the Gamma or lognormal distribution be used to estimate TTD for teclistamab arm?

Switching from a teclistamab Q1W to a Q2W regimen

- Is the EAG's approach to model patients switching from teclistamab Q1W to Q2W regimen at 52 weeks appropriate for decision making?

Utility values

- Which approach to inform utility values for PomDex arm are more appropriate?
  - Values accepted by NICE in TA510 and TA783 **– Company base case**
  - MajesTEC-1 EQ-5D data **– EAG base case**

ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; Q1W: Once weekly; Q2W: Every two weeks; TTD: Time to treatment discontinuation

Key issues and questions for committee

Cost effectiveness issues
Costs of immunoglobulin use • How many doses and what proportion of patients should receive IVIG in the economic model?
Drug wastage • What proportion of teclistamab wastage should be used in the economic model?

ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; Q1W: Once weekly; Q2W: Every two weeks; TTD: Time to treatment discontinuation

Teclistamab for treating relapsed or refractory multiple myeloma after 3 treatments

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

	Final scope	Company	EAG comments
Population	People with relapsed or refractory multiple myeloma (RRMM) after ≥3 prior treatments including an IMiD, a PI and an anti-CD38 Ab and have demonstrated disease progression on the last treatment	As per NICE scope	As per NICE scope
Intervention	Teclistamab	As per NICE scope	As per NICE scope
Comparators	• 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	Clinical advice to the EAG agrees that PomDex is the most relevant comparator for this appraisal
Outcomes	OS, PFS, Response rates, AEs of treatment and HRQoL	As per NICE scope	As per NICE scope

AEs: Adverse events; HRQoL: Health-related quality of life; OS: Overall survival; PFS: Progression-free survival

Key clinical trial: MajesTEC-1 study design

Phase I/II, open-label, multicentre, international single-arm trial of teclistamab monotherapy for patients with TCE RRMM who have received at least 3 prior lines of treatment including an IMiD, a PI, and an anti-CD38 mAb

Figure 6: MajesTEC-1 study design

Source: Company submission, Figure 8

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IMiD: Immunomodulatory agent; PI: Proteasome inhibitor; RP2D: Recommended phase II dose; SC: Subcutaneous; TCE: Triple class exposed

Key clinical effectiveness evidence: overview

MajesTEC-1 and UK RW TCE RRMM study designs and outcomes

	MajesTEC-1: all treated analysis set (N=165)	UK RW TCE RRMM: PomDex ECOG PS 0/1 (N=645)
Design	Phase I/II, open-label, single-arm, multicentre	Retrospective, descriptive, non-interventional registry
Population	Adults with RRMM previously treated with an IMiD, PI and mAb	Adults with RRMM previously treated with three or more of PI, an IMiD and an anti-CD38 mAb
Intervention	Teclistamab	Pomalidomide plus dexamethasone (PomDex)
Comparator	N/A	N/A
Duration	Median follow up: 30.4 months	Median follow up: 26 months
Data cut off	August 2023	March 2023
Primary outcome	Overall response rate	OS and TTNT
Other outcomes	DoR, OS, PFS, MRD negativity rate, HRQoL and AEs	
Locations	**Phase I:** France, Netherlands, Spain, Sweden, US **Phase II:** UK, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, US, Canada, China	UK

Source: Company submission, Table 4 and 22

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AEs: Adverse events; DoR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status HRQoL: Health-related quality of life; IMiD: Immunomodulatory agent; MRD: Minimal residual disease; N/A: Not applicable; OS: Overall survival; PFS: Progression-free survival; PI: Proteasome inhibitor; PomDex: Pomalidomide plus dexamethasone; RRMM: Relapsed or refractory multiple myeloma; TTNT: Time to next treatment

Baseline characteristics: MajesTEC-1 and UK RW TCE RRMM

MajesTEC-1 and UK RW TCE RRMM study baseline characteristics

		MajesTEC-1: all treated analysis set (N=165)	UK RW TCE RRMM: PomDex ECOG PS 0/1 (N=645)
Age, median (range), years		64.0 (33 to 84)	72.7 (65.4 to 78.0)
Male, n (%)		96 (58.2)	368 (57.1)
Time since diagnosis, median (range) years		6.0 (0.8 to 22.7)	4.4 (3.2 to 5.8)
Previous lines of treatment, median (range)		5 (2 to 14)	4 (3 to 7)
Extramedullary disease, n/N (%)		28/165 (17.0)	NR
ISS, n/N (%)	I	85/162 (52.5)	58/645 (9.0)
	II	57/162 (35.2)	73/645 (11.3)
	III	20/162 (12.3)	85/645 (13.2)
	Unknown	NR	429/645 (66.5)
ECOG PS	0	55 (33.3)	133 (20.6)
	1	[redacted]	512 (79.4)
	2 to 4	[redacted]	NA
High risk cytogenetic profile, n/N (%)		[redacted]	NR
Prior ASCT, n (%)		[redacted]	225 (34.9)
Prior anti-BCMA treatment, n (%)		0 (0)	NR

Source: EAG report, Table 9

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NICE

ASCT: Autologous stem cell transplantation; BCMA: B cell maturation antigen; ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International staging system; NA: Not applicable; NR: Not reported

Teclistamab real world evidence

Results from teclistamab real world evidence studies (Dima 2023 and Riedhammer 2024)

	Dima US retrospective study (N=106)	Riedhammer German retrospective study (N=123)
Population	TCE RRMM	TCE RRMM
Median follow-up, months	3.8	5.5
ORR (95% CI)	66 (NR)	59.3 (NR)
Median PFS, months (95% CI)	5.4 (3.4 to NE)	8.7 (NR)
Median TTNT, months (95% CI)	NR	NR
Median OS, months (95% CI)	NE	NE

Source: EAG report, Table 10

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CI: Confidence interval; NE: Not estimated; NR: Not reported; ORR: Overall response frate; OS: Overall survival; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TCE RRMM: Triple-class exposed relapsed or refractory multiple myeloma; TTNT: Time to next treatment

Adverse events: MajesTEC-1

MajesTEC-1 study adverse events rates

Adverse event category	MajesTEC-1: all treated analysis set (N=165)
Any serious adverse event, n (%)	[redacted]
Any death, n (%)	[redacted]
Deaths related to study treatment, n (%)	[redacted]
Any treatment-related adverse event, all grades, n (%)	[redacted]
Any treatment-related adverse event, grade 3 / 4, n (%)	[redacted]
Cytokine release syndrome (CRS), all grades, n (%)	119 (72.1)
CRS, grade 3 / 4, n (%)	1 (0.6)
Immune-effector cell-associated neurotoxicity syndrome (ICANS), all grades, n (%)	[redacted]

Source: EAG report, Section 3.7

EAG comments:

- Dima study and Riedhammer study safety results were largely consistent with the MajesTEC-1 trial safety results
- Safety and tolerability data for PomDex were not collected in the UK RW TCE RRMM study
  - Clinical advice to the EAG suggests that CRS and ICANS are not associated with PomDex treatment and adverse events are more common with teclistamab than other RRMM treatments but can be managed routinely in NHS clinical practice

PomDex: Pomalidomide plus dexamethasone; RRMM: Relapsed or refractory multiple myeloma

ITC method - identification of co-variates

Only one of five priority co-variates had sufficient IPD from UK RW TCE RRMM

- Company base case analysis is based on re-weighting using 5-varialble adjustment
  - Initially six of 17 potential covariates identified were considered for adjustment.
  - ASCT was removed from the weighting process as no statistically significant differences in OS or TTNT was found between people with or without prior ASCT ➔ Clinical advice to company suggested that ASCT is one of the lowest priority prognostic co-variates and is highly correlated with age

Priority co-variates and co-variates with IPD from UK RW TCE RRMM study

Rank	Factor	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	Prior stem cell transplant	Yes
Non-priority	ECOG PS	Yes

Source: EAG report, Table 13

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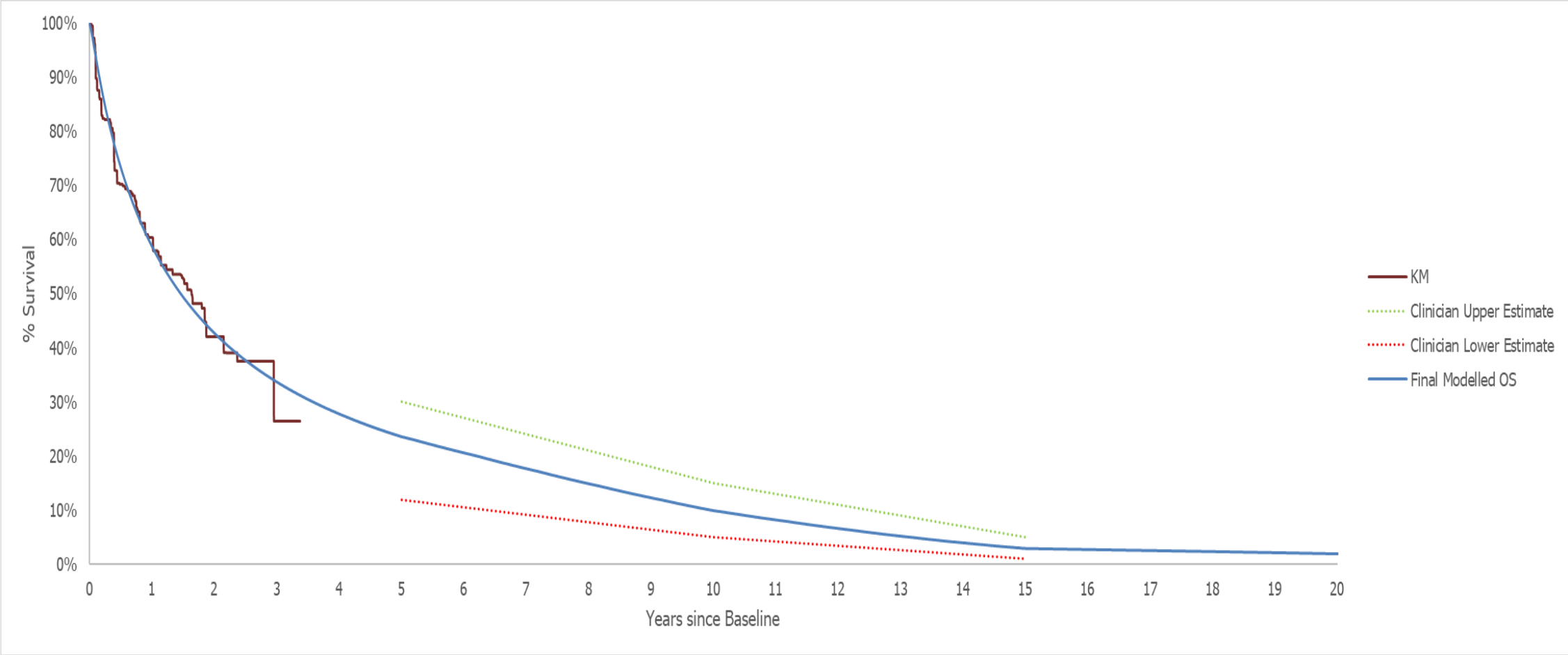
ASCT: Allogenic stem cell transplant; ECOG PS: Eastern Cooperative Oncology Group performance status; IPD: Individual patient data; ISS: International staging system; LOTs; Lines of treatments; OS: Overall survival; TTNT: Time to next treatment

Long term OS estimates – teclistamab arm

Figure 7: Attenuated log-normal extrapolation fitted to the subsequent treatment adjusted OS KM data from MajesTEC-1



Source: Company submission, Figure 40

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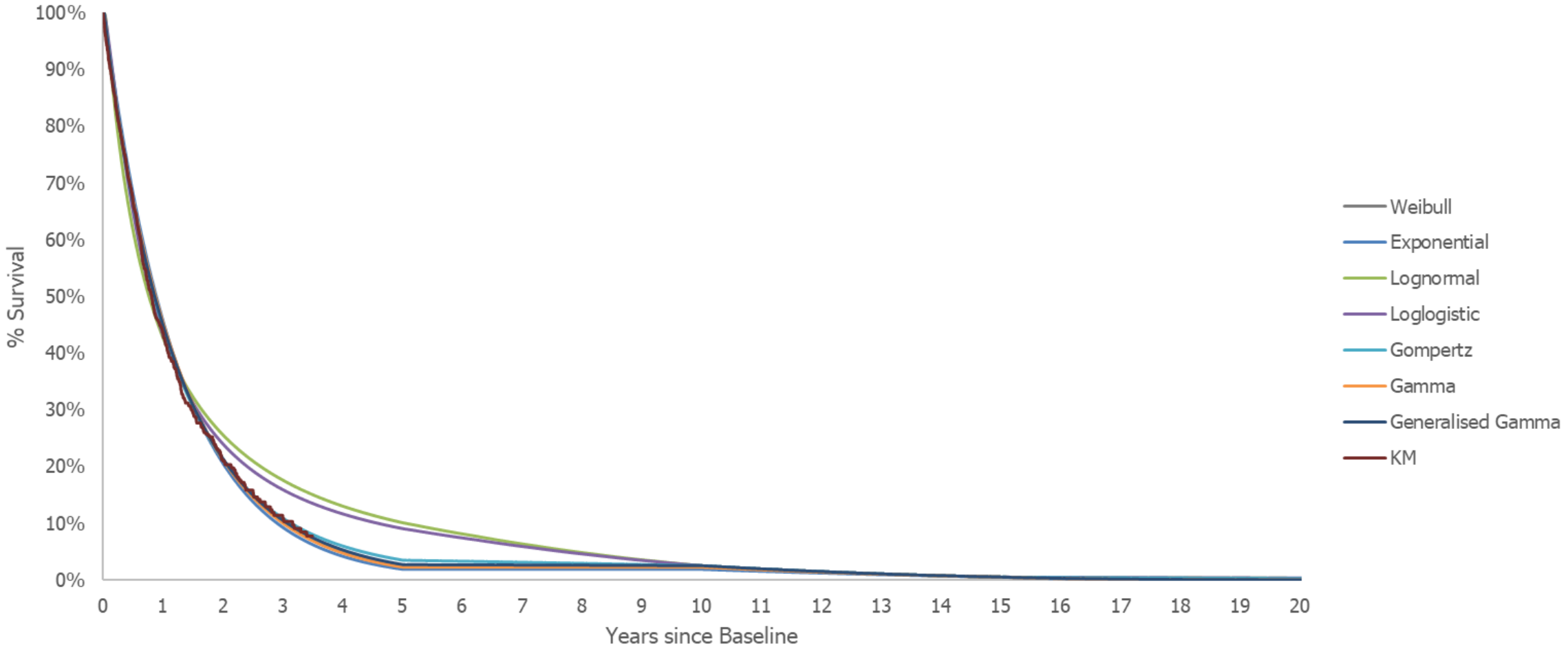
KM: Kaplan-Meier; OS: Overall survival

Long term OS estimates – PomDex arm

Figure 8: Extrapolation of attenuated OS for PomDex using IPD from the UK RW TCE RRMM



Source: Clarification response, Figure 1

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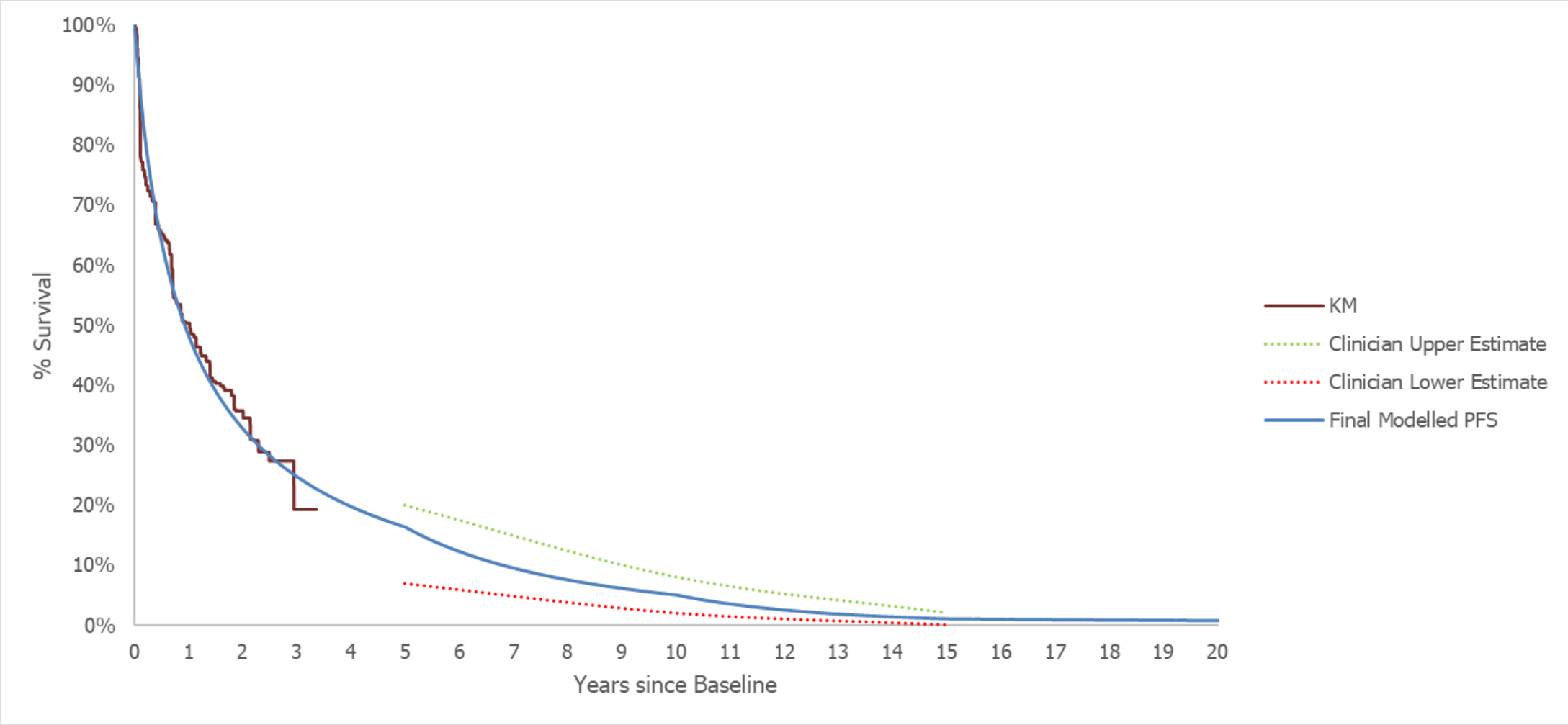
IPD: Individual patient data; KM: Kaplan-Meier; OS: Overall survival; PomDex: Pomalidomide plus dexamethasone

Long term PFS estimates – teclistamab arm

Figure 9: Attenuated log-normal extrapolation fitted to the PFS KM data from MajesTEC-1



Source: Company submission, Figure 44

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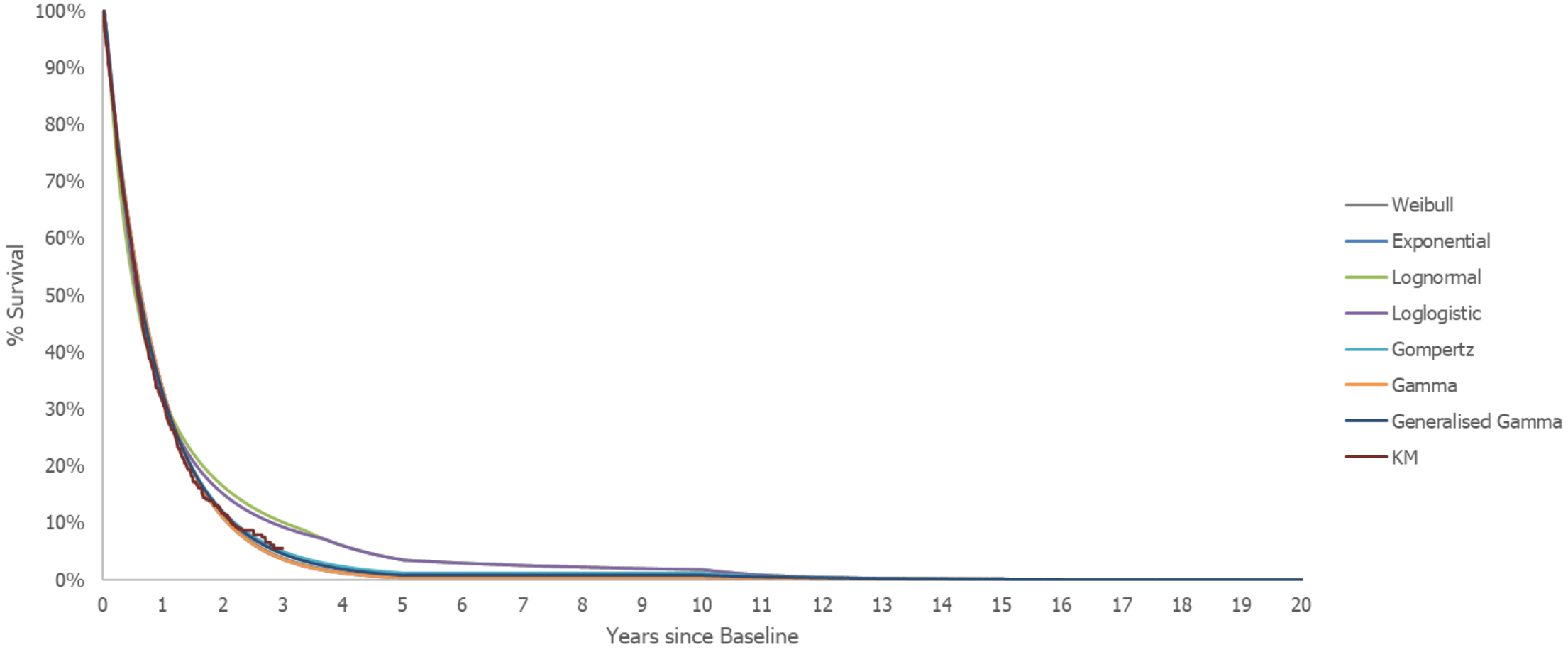
KM: Kaplan-Meier; PFS: Progression-free survival

Long term PFS estimates – PomDex arm

Figure 10: Extrapolation of attenuated PFS (as proxy for TTNT) for PomDex using IPD from the UK RW TCE RRMM



Source: Clarification response, Figure 2

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IPD: Individual patient data; KM: Kaplan-Meier; PFS: Progression-free survival; PomDex: Pomalidomide plus dexamethasone; TTNT: Time to next treatment

Long term TTD estimates – teclistamab arm

Figure 11: Extrapolation of TTD for teclistamab using IPD from MajesTEC-1

Source: Company submission, Figure 47

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IPD: Individual patient data; KM: Kaplan-Meier; TTD: Time to treatment discontinuation

Long term TTD estimates – PomDex arm

PomDex TTNT KM and extrapolation overlaid with the derived TTD curve

Source: Company submission, Figure 48

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KM: Kaplan-Meier; PomDex: Pomalidomide plus dexamethasone; TTD: Time to treatment discontinuation; TTNT: Time to next treatment

Teclistamab skipped doses

See: Differences between company and EAG base case assumptions

Company

- [redacted] of teclistamab maintenance doses were assumed to be missed in the company model
  - applied from cycle 2 onwards in the model as no patients missed a step-up dose in MajesTEC-1

EAG comments

- Prefers [redacted] for teclistamab skipped doses in maintenance phase ➔ aligned with MajecTEC-1 data
- Company's approach uses the percentage of all doses [loading and maintenance] missed in MajesTEC-1

Company response

- Patients with dose delays were not recorded as skipped doses in the trial
- Number of expected doses was based on the date of treatment discontinuation or last trial observation
- There is difference in permitted teclistamab dose frequency in the MajesTEC-1 trial compared to the teclistamab licence wording

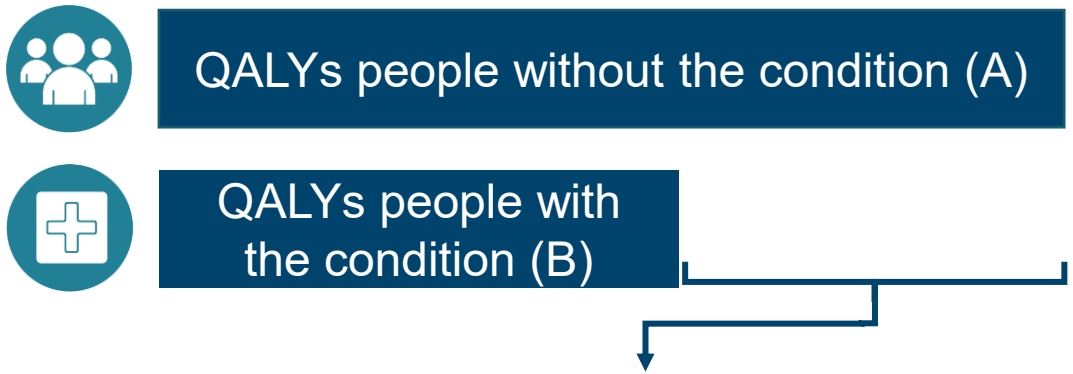
EAG critique

- Delayed doses are not the same as missed doses and should not be considered as skipped doses
  - Delayed doses were not recorded as skipped doses in the MajecTEC-1 trial
- If teclistamab licensed dosing schedule had been implemented in the MajesTEC-1 trial, the effects on time on treatment, skipped doses and outcomes are unknown

Is the EAG's approach to teclistamab skipped doses in the economic model more appropriate than company's approach?

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

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QALY: Quality-adjusted life year

QALY weightings for severity (2/2)

Company

Company's QALY shortfall analysis

Component	QALYs / shortfall
Expected total QALYs for the general population	[redacted]
Total QALYs that people living with a condition would be expected to have with current treatment (PomDex)	[redacted]
QALY shortfall (absolute)	[redacted]
QALY shortfall (proportional)	[redacted]

Proportional shortfall is between 0.85 and 0.95 therefore a severity weighting of 1.2 applies

EAG comments

- Agrees 1.2 QALY weighting is appropriate

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PomDex: Pomalidomide plus dexamethasone ; QALY: Quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.