Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies (ID5082)

Committee slides – contains [redacted] information

Technology appraisal committee C [14 October 2025]

Chair: Richard Nicholas

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Company: Johnson & Johnson Innovative Medicine

Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ✓ **ACM1 recap and DG consultation responses**
- ❑ Clinical effectiveness evidence
- ❑ Cost effectiveness evidence
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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See appendix: Treatment pathway

Talquetamab (Talvey, Johnson & Johnson Innovative Medicine)

Marketing authorisation	MHRA approval granted on 9 October 2023 for use *"as a monotherapy for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy"*
Mechanism of action	Humanised immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody that binds to cluster of differentiation (CD) 3 receptors expressed by T cells and G protein-coupled receptor class 5D (GPRC5D), a novel target expressed on the surface of malignant multiple myeloma cells, and redirects CD3+ T cells to GPRC5D-expressing tumour cells to kill them
Administration	Subcutaneous injection • 0.4mg/kg once weekly or 0.8mg/kg every two weeks
Price*	• The list price for talquetamab is £326.41 (2mg vial) and £4,352.00 (40mg vial) • Annual price for year 1 is £177,020 (includes priming dose) and year 2 onward is £165,816 (excludes priming dose) • Company has a confidential PAS discount in place ➔ Increased after ACM1

* Talquetamab pricing per person is based on the mean weight of participants and drug wastage. The company's model assumed that the average weight of people is [redacted] kg

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IMiD: Immunomodulatory agent; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: Patient access scheme; PI: Proteasome inhibitor; RRMM: Relapsed or refractory multiple myeloma

ACM1 recommendations and key conclusions

"Talquetamab should not be used to treat relapsed and refractory multiple myeloma in adults when:

- **they have had 3 or more treatments including:**
  - **an immunomodulatory agent**
  - **a proteasome inhibitor, and**
  - **an anti-CD38 antibody, and**
- **the multiple myeloma has progressed on the last treatment"**

ACM1 key conclusions/considerations		Company update?	Resolved/ To discuss
Talquetamab clinical effectiveness evidence	• Clinical-effectiveness evidence for talquetamab from MonumenTAL-1 is appropriate	N/A	-
	• Committee would like to see results from clinical-effectiveness analyses of all cohort A* and cohort C[Ŧ] (cohort A+C) data from MonumenTAL-1 pooled, and the related economic analyses	Scenario analyses	To discuss
	• Company to present ITC for the clinical effectiveness of talquetamab informed using analyses of all data from MonumenTAL-1 cohort A+C pooled	Scenario analyses	To discuss

NICE *Cohort A had weekly treatment, [Ŧ]cohort C had treatment every 2 weeks

ACM: Appraisal committee meeting; ITC: Indirect treatment comparison; N/A: Not applicable

RECAP

ACM1 key conclusions (2)

ACM1 key conclusions/considerations (continued)		Company update?	Resolved/To discuss
ITC OS results	• OS HR for talquetamab compared with teclistamab from the ITC is highly uncertain	N/A	-
	• There was no clear explanation for the early separation of the OS curves despite minimal separation in the curves for DoR and PFS	Further information	To discuss
	• No clear explanation for the lack of correlation between PFS and OS results from the ITC	Further information	To discuss
	• Company to present a survival analysis censoring for deaths related to COVID-19	Updated base case	To discuss
Economic model	• Discounting from year 2 onward and the exclusion of the half-cycle correction is appropriate	Updated base case	Resolved
Long-term extrapolations were uncertain	• Would like to see the long-term OS, PFS and TTD extrapolations modelled independently for both teclistamab and talquetamab without calibrating to clinical-expert estimates	Updated base case and scenario analyses	Committee to confirm resolved

ACM: Appraisal committee meeting; DoR: Duration of response; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

RECAP

ACM1 key conclusions (3)

ACM1 key conclusions/considerations (continued)		Company update?	Resolved/ To discuss
Subsequent treatments should be appropriately modelled (costs and benefits)	• Costs and benefits of both subsequent talquetamab and subsequent teclistamab following initial treatment should be modelled	Updated base case	Committee to confirm resolved
	• Company to provide a more detailed explanation of overall methods used to adjust for subsequent treatments not available in the NHS	Further information	Committee to confirm resolved
	• Would like to see analyses using parametric models, other than the Weibull model, when adjusting for subsequent treatments using the 2-stage adjustment approach	Further information	Committee to confirm resolved
IVIg use	• The proportion of IVIg use in the talquetamab arm based on MonumenTAL-1 and in the teclistamab arm based on MajesTEC-1 is appropriate	Updated base case	Resolved
	• IVIg use should be modelled for subsequent talquetamab and teclistamab treatments	Updated base case	Resolved
AE disutilities	• Company to provide more explicit modelling of adverse-event disutilities and include the impact of altered taste and associated weight loss in the adverse-event disutility for talquetamab	Updated base case	Resolved

ACM: Appraisal committee meeting; AE: Adverse event; IVIg: Intravenous immunoglobulin

Key issues and questions for committee

Clinical effectiveness issues

Talquetamab clinical effectiveness evidence

- Is clinical effectiveness of talquetamab from cohort C alone or larger pooled cohort A+C of MonumenTAL-1 more appropriate for decision making?
- Do the additional scenarios provided by the company using pooled cohort A+C reduce the uncertainty in the clinical evidence and ITC results?

ITC OS results: COVID-19 impact

- Is the company's OS HR censoring for deaths related to COVID-19 appropriate?
- Do either of company's approaches for censoring for deaths related to COVID-19 reduce the uncertainty in the ITC OS results?

ITC OS results: early separation of the OS curves

- Does the additional information provided by the company on early separation of talquetamab and teclistamab OS curves reduce the uncertainty in the ITC OS results?

ITC OS results: lack of correlation between PFS and OS

- Does the additional information provided by the company on the correlation between PFS and OS reduce the uncertainty in the ITC OS results?

Cost-effectiveness issues- largely resolved. Committee to confirm

Modelling OS, PFS and TTD

- Is the company's modelling using HR-based approach applied to uncalibrated Weibull distribution appropriate?

Subsequent treatments

- Do these analyses reduce uncertainty in the subsequent treatment adjustment?

HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Consultation responses summary

1. **Myeloma UK**
   - OS benefit and innovation, talquetamab dosing and side effects (altered-taste)
2. **UK Myeloma Society:**
   - Recommendations limit access, OS benefit, regression analyses, infection risk, talquetamab dosing and novel mechanism of action
3. **J&J (company)**
   - ITC, OS benefit, Covid-19 impact, long-term extrapolations, disutility (altered-taste), uncaptured benefits

See appendix: Updates in company base case post ACM1

ACM: Appraisal committee meeting; ITC: Indirect treatment comparison; OS: Overall survival

Consultation responses – stakeholder comments

Myeloma UK and UK Myeloma Society

- **Current recommendations may limit access to talquetamab at 4th line for TCE RRMM**, especially as BCMA therapies move earlier in the treatment pathway, reducing future options for these patients
- **Infection risk is significantly lower with talquetamab compared to BCMA-targeting bispecific antibodies (e.g. teclistamab)**, with grade ≥3 infections occurring at half the rate (1.5% versus 3% per month), addressing a critical unmet need
- **Dosing every 2 weeks for talquetamab better reflects patient preference and real-world practice**
- **Taste-related side effects from talquetamab have a manageable impact on quality of life**
- **Caution should be applied when using Cartier et al. 2015 and Etekal et al. 2021 regression analysis** which are not studied with bispecific therapies with a novel mechanism of action

BCMA: B-cell maturation antigen; RRMM: Relapsed or refractory multiple myeloma; TCE: Triple-class exposed

Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ❑ ACM1 recap and DG consultation responses
- ✓ **Clinical effectiveness evidence**
- ❑ Cost effectiveness evidence
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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Talquetamab clinical effectiveness evidence (1)

ACM1 considerations

- Committee would like to see pooled results from **MonumenTAL-1 cohort A+C data**, and the related economic analyses, including the ITC for the comparative clinical effectiveness of talquetamab versus teclistamab
  - **Cohort A** included patients receiving a **once weekly dosing** regimen of talquetamab
  - **Cohort C** included patients receiving **every 2 weeks dosing** regimen of talquetamab

Company DG consultation response

- **Provided pooled ITC analyses using cohorts A+C**, included naïve unadjusted, and weighted 10:90 cohort A+C. Latter analyses were with and without COVID-19 censored deaths. Results are consistent with the company's base case using cohort C alone.
- **Cohort C (every 2 weeks dosing) is most relevant to UK clinical practice**, reflecting patient preference, reduced healthcare burden, and improved safety and efficacy
  - **Weighted 10:90 cohort A+C ITC analysis aligns with clinical expectations**, as only approximately 10% of patients are expected to receive weekly dosing ➔ This is a conservative approach
- **Unadjusted cohort A+C data show comparable PFS and TTD to teclistamab**, but a notable OS benefit for talquetamab, though less reflective of real-world use
- **Differences in efficacy between cohorts A and C are supported by clinical data**, with cohort C showing longer treatment duration and reduced T cell exhaustion, contributing to better outcomes

ACM: Appraisal committee meeting; DG: Draft guidance; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Talquetamab clinical effectiveness evidence (2)

Results of the additional ITC analyses between talquetamab (pooled, unweighted cohort A+C and pooled, 10:90 weighted cohort A+C) and teclistamab (before and after ATT weighting*)

	Naïve (pooled, unweighted cohort A+C) N=297	Adjusted		
		ATT (cohort C) N= 154	ATT (pooled, unweighted cohort A+C) N= 297	ATT (pooled, 10:90 weighted cohort A+C) N= 153
PFS HR (95% CI) (p-value)				
OS[a] HR (95% CI) (p-value)				
TTD HR (95% CI) (p-value)				

[a] Results for OS include adjustments for subsequent treatments not available in UK clinical practice and the inclusion of talquetamab post-teclistamab and teclistamab post-talquetamab

Company base case **Scenario analyses**

*ATT adjustment estimates the average treatment effect of teclistamab in the population that received talquetamab, typically by reweighting individual patient data to match the characteristics of the treated population. In this case the MajesTEC-1 (teclistamab) cohort was reweighted to mimic MonumenTAL-1 (talquetamab).

 ATT: Average treatment effect for the treated; CI: Confidence interval; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Talquetamab clinical effectiveness evidence (3)

EAG critique

- **Pooled cohort A+C ITC HRs were not used in the company's updated base case ➔** 10:90 weighted scenario analysis provided by company was consistent with the updated base case (cohort C with COVID-19 censoring)
- EAG replicated ITCs using pooled, unweighted data from cohorts A + C of MonumenTAL-1 produced the HRs for PFS, OS, and TTD that are visually consistent with cohort C alone
- Clinical experts previously noted that cohort C dosing (every 2 weeks) is more suitable for UK practice than cohort A (once every week) dosing ➔ Results in reduced time at treatment centres

See appendix: MonumenTAL-1 study design, MonumenTAL-1 and MajesTEC-1 study designs, Baseline characteristics: MonumeTAL-1 and MajesTEC-1 and Key results: MonumenTAL-1 and MajesTEC-1

- Is clinical effectiveness of talquetamab from cohort C alone or larger pooled cohort A+C of MonumenTAL-1 more appropriate for decision making?
- Do the additional scenarios provided by the company using pooled cohort A+C reduce the uncertainty in the clinical evidence and ITC results?

HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

ACM1: Regression analyses of studies that reported OS and PFS HRs between MM treatments

EAG- The talquetamab versus teclistamab ITC HR for PFS [redacted] and OS [redacted] appears as an outlier

Company- Etekal et al. states that "As no randomised trials have yet [been] reported for other agents such as bispecific agents and chimeric antigen receptor therapy, our results may not be applicable to those settings

NICE Methods Manual 4.6.17 When outcomes are known to be related, a joint synthesis of structurally related outcomes is recommended whenever possible, to increase precision and robustness of decision making.

ACM: Appraisal committee meeting; HR: Hazard ratio; ITC: Indirect treatment comparison; MM: Multiple myeloma; OS: Overall survival; PFS: Progression-free survival; POM+DEX: Pomalidomide plus dexamethasone

ITC OS results: COVID-19 impact (1)

ACM1 considerations

- OS HR [redacted] for talquetamab compared with teclistamab from the ITC is highly uncertain
  - ➢ Company to present a survival analysis censoring for deaths related to COVID-19

Company DG consultation response

- **COVID-censored ITC analyses confirm the OS benefit of talquetamab** ➔ OS benefit not solely due to differences in COVID-19-related deaths between MonumenTAL-1 and MajesTEC-1 trials
- **Two censoring approaches were used:**
  - Only patients with COVID-related deaths who had CR and no disease progression (**base case**) ➔ Minimizes selection bias by excluding patients with a favourable prognosis only
  - All patients with COVID-related deaths (**scenario**)
- **Consistent OS benefit was observed across all analyses**, including both censoring approaches and across different cohorts (cohort C [**base case**] and weighted cohort A+C [**scenario**])

Comparison of OS HR between talquetamab (cohort C) vs teclistamab (ATT-adjusted) with different COVID adjustment

	ATT adjusted		
	Non-COVID-19 censored	COVID censored (base case analysis)	COVID censored (alternative approach)
OS HR (95% CI) (p-value)	[redacted]	[redacted]	[redacted]

ACM: Appraisal committee meeting; ATT: Average treatment effect for the treated; CI: Confidence interval; CR: Complete response; DG: Draft guidance; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival

ITC OS results: COVID-19 impact (2)

See appendix: COVID-19 timeline and COVID-19 impact

EAG critique

- Company's comparison between talquetamab and teclistamab is undermined by unequal COVID protection across cohorts ➔ Assessment of the lack of vaccination for COVID in teclistamab recipients seems mandatory for a reliable comparison between talquetamab and teclistamab
- Re-analysis censoring COVID-related deaths was conducted, but this approach is limited and may underestimate the broader impact of COVID on OS
- Despite high COVID-related mortality in the teclistamab arm, censoring had minimal effect on OS HRs, which raises concerns about the adequacy of COVID-19 impact adjustment
- With access to individual patient data, the company could explore more robust analyses, such as comparing vaccinated and unvaccinated subgroups across both trials
- Given company considers teclistamab recipients are more susceptible to infection compared with talquetamab and the lack of COVID-19 vaccination in MajesTEC-1 and non-prophylactic use of IVIg, 'those who received treatment' may be more appropriate analysis than 'intention to treat'

- Is the company's OS HR censoring for deaths related to COVID-19 appropriate?
- Do either of company's approaches for censoring for deaths related to COVID-19 reduce the uncertainty in the ITC OS results?

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HR: Hazard ratio; IVIg; Intravenous immunoglobulin; OS: Overall survival

ITC OS results: early separation of the OS curves

ACM1 considerations

- OS HR [redacted] for talquetamab compared with teclistamab from the ITC is highly uncertain
  - ➢ No clear explanation for the early separation of the OS curves, minimal separation for DoR and PFS

Company DG consultation response

- The OS curves show a notable early separation, with fewer deaths in the first three months for talquetamab-treated patients compared to teclistamab, largely driven by lower rates of disease progression and infections

Number of deaths during the first three months of the MonumenTAL-1 and MajesTEC-1 trials

	Talquetamab (MonumenTAL-1 cohort C; N=154)	Teclistamab (MajesTEC-1; N=165)
Death, n (%)	[redacted]	[redacted]
Reasons for death:		
Progressed disease	[redacted]	[redacted]
AE:	[redacted]	[redacted]
• COVID-19	[redacted]	[redacted]
• Other AEs	[redacted]	[redacted]
Other	[redacted]	[redacted]

 ACM: Appraisal committee meeting; AE: Adverse event; DG: Draft guidance; DoR: Duration of response; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival

ACM1 Recap- Duration of response (DoR) and Progression-free Survival (PFS) KM curves from the ITC results

DoR (Figure A) and PFS (Figure B) Kaplan–Meier (K–M) curves for talquetamab and teclistamab (before and after ATT weighting) from ACM1

Figure A- DoR

Figure B- PFS

ACM1 committee conclusion: No statistically significant benefit in duration of response or progression-free survival

ACM: Appraisal committee meeting; CI: Confidence Interval; DoR: Duration of response; HR: Hazard ratio; ITC: Indirect treatment comparison; KM: Kaplan Meier; OS: Overall survival; PFS: Progression-free survival

See appendix: ITC results at ACM1 – Overall survival

ITC OS results: early separation of the OS curves

Figure showing COVID-19 related death censored OS KM curves for talquetamab (MonumenTAL-1 Cohort C) and teclistamab (**updated base case approach**; ATT-adjusted analysis, incorporating subsequent treatment adjustment)

[redacted]

OS HR [95% CI]

[redacted]

- Does the additional information provided by the company on early separation of talquetamab and teclistamab OS curves reduce the uncertainty in the ITC OS results?

ATT: Average treatment effect for the treated; HR: Hazard ratio; ITC: Indirect treatment comparison; KM: Kaplan Meier; OS: Overall survival

ITC OS results: lack of correlation between PFS and OS (1)

ACM1 considerations

- OS HR ([redacted]) for talquetamab compared with teclistamab from the ITC is highly uncertain
  - ➢ No clear explanation for the lack of correlation between PFS and OS results from the ITC

Company DG consultation response

- **Preservation of humoral immunity:** Talquetamab targets GPRC5D, which spares B cells and plasma cells, leading to better immune recovery and lower rates of severe infections compared to BCMA-targeting therapies like teclistamab
- **Reduced T cell exhaustion:** Talquetamab's dosing schedule (every two weeks) allows for treatment-free intervals that help preserve T cell function, improving response to subsequent therapies and contributing to longer survival
- **Talquetamab shows improved PFS2 outcomes compared to teclistamab**

Comparison of PFS2 between talquetamab (cohort C) and teclistamab (before and after ATT weighting; including subsequent talquetamab and teclistamab)

Comparison	PFS2 HR (95% CI) (p-value)
Naïve	[redacted]
Weighting	
ATT + subsequent treatment adjustment + inclusion of talquetamab post-teclistamab and teclistamab post-talquetamab	[redacted]

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ACM: Appraisal committee meeting; ATT: Average treatment effect for the treated; DG: Draft guidance; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival

ITC OS results: lack of correlation between PFS and OS (2)

EAG critique

- Concerns about using concept of PFS2 because it is not adjusted for COVID-related deaths. Some people may have survived but experienced worsened prognosis, which may bias results
- Used reliance on investigator assessment rather than independent assessment

Table showing causes of death due to progressive disease

Death, N (%)	Talquetamab	Teclistamab
	MonumenTAL-1 Cohort C [N=154]	MajesTEC-1 [N=165]
Total deaths	[redacted]% of all patients)	[redacted]% of all patients)
Deaths due to PD	[redacted]**% of those who died)**	[redacted]**% of those who died)**
Deaths due to AE	[redacted]% of those who died)	[redacted]% of those who died)
Not study drug related	[redacted]% of those who died or [redacted]% of all AE-related deaths)	[redacted]% of those who died or [redacted]% of all AE-related deaths)
Study drug related	[redacted]	[redacted]% of those who died)
Infection related deaths	[redacted]**% of those who died)**	[redacted]**% of those who died, or [redacted]% of all AE-related deaths)**
Non-infection AE deaths	[redacted]% of those who died)	[redacted]% of those who died)
Other	[redacted]% of those who died)	[redacted]% of those who died)

- Does the additional information provided by the company on the correlation between PFS and OS reduce the uncertainty in the ITC OS results?

ACM: Appraisal committee meeting; AE: Adverse event; ITC: Indirect treatment comparison; OS: Overall survival; PD: Progressed disease; PFS: Progression-free survival

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Summary of model outputs (1)

Markov trace showing OS, PFS and time on treatment for teclistamab and talquetamab over model time horizon

ACM: Appraisal committee meeting; OS: Overall survival; PFS: Progression-free survival

Summary of model outputs (2)

OS Markov trace showing teclistamab and talquetamab life years gained over model time horizon

Table: Disaggregated life years gained in progression-free and post-progression states

	Life years gained		
	Progression-free	Post-progression	Overall
Talquetamab	[redacted]	[redacted]	[redacted]
Teclistamab	[redacted]	[redacted]	[redacted]

Are the model outcomes appropriate?

ACM: Appraisal committee meeting; OS: Overall survival; PFS: Progression-free survival

Modelling OS, PFS and TTD

ACM1 considerations

- Requested long-term OS, PFS and TTD extrapolations modelled independently for both teclistamab and talquetamab without using clinical-expert calibration

Company DG consultation response

- Updated base case- teclistamab OS, PFS and TTD extrapolated using the uncalibrated Weibull curve to align with EAG and committee
- Provided scenarios independently modelling talquetemab OS, PFS and TTD using various distributions (e.g. Weibull, Gamma, lognormal)
- These show minimal impact on the ICER compared to the HR approach, with most results remaining close to or below the £30,000/QALY threshold
- Maintained HR approach more appropriate to derive talquetamab outcomes: PH assumption is valid, directly incorporates robust ITC results, introduces less uncertainty than independent modelling

EAG critique

- Company adopted EAG preferred Weibull extrapolation for teclistamab long-term survival outcomes
- Company noted that all the scenarios with independently applied survival extrapolations led to small increases in incremental costs, over the HR approach
- Agree a HR approach is appropriate to model talquetamab outcomes; do not agree with the HR values

See appendix: Modelling OS, PFS and TTD at ACM1 and Modelling OS, PFS and TTD - company scenarios

ACM: Appraisal committee meeting; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; PH: Proportional Hazards; QALY: Quality-adjusted life years; TTD: Time to treatment discontinuation

Subsequent treatments (1)

ACM1 considerations

- Costs and benefits of subsequent talquetamab and subsequent teclistamab should be modelled in both arms
- Requested more detailed explanation of overall methods used to adjust for subsequent treatments not available in the NHS
- Requested analyses using parametric models, other than the Weibull model, when adjusting for subsequent treatments using the 2-stage adjustment approach

Company DG consultation response

- In base case:
  - Costs and benefits of subsequent talquetamab and teclistamab
  - Two-stage OS adjustment using Weibull curve to remove effects of subsequent treatments not routinely available in the UK.
- Provided scenarios using alternative parametric distributions (e.g. Exponential, Gamma, lognormal)
- Showed consistent acceleration factors and OS HRs ➔ the distribution choice to adjust for subsequent treatment has negligible impact on the ITC results

ACM: Appraisal committee meeting; DG: Draft guidance; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; TSD: Technical Support Document

Subsequent treatments (2)

EAG critique

- Company's exploration has minimised uncertainty with this adjustment- shows visual consistency between alternative parametric models, and in the results of using the Weibull distribution in the AFT model.
- Not clear why company select AFT Weibull rather than proportional hazards Weibull to apply time constant ITC HR ratio. However, as the 2 Weibull models are visually consistent then this is plausible.

OS HRs for talquetamab (cohort C) vs teclistamab (before and after ATT weighting; including subsequent talquetamab and teclistamab) with different distributions

Comparison	OS HR (95% CI)	p-value
Naïve	[redacted]	[redacted]
ATT + subsequent treatment adjustment		
Exponential	[redacted]	[redacted]
Weibull (unchanged Company base case)	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]

- Do these analyses reduce uncertainty in the subsequent treatment adjustment?

AFT: Accelerated Failure Time; ATT: Average treatment effect for the treated; Confidence interval; DoR: Duration of response; HR: Hazard ratio; ITC: Indirect Treatment Comparison; OS: Overall survival

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- ❑ Modelling and cost effectiveness evidence
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Summary of assumptions in the company base case and EAG's scenario analyses

Committee's preferred assumptions in draft guidance		Company base case	EAG scenarios
Subsequent treatment	Including in the model the costs and benefits of using subsequent talquetamab and subsequent teclistamab after initial treatment	Included	Included
IVIg use	• The proportions having IVIg use in the talquetamab arm being based on MonumenTAL-1 data and in the teclistamab arm being based on MajesTEC-1 data • IVIg use being modelled for subsequent talquetamab and teclistamab treatments	Included	Included
Economic model	• Discounting for costs and QALYs from the second year of the model • The exclusion of half-cycle correction of costs and QALYs in the economic model	Included	Included
Company updates post draft guidance			
ITC OS HR	**Censored for COVID-19 deaths**	**Included**	**Excluded**
Modelling OS, PFS and TTD	Uncalibrated Weibull for teclistamab arm	Included	Included
AE disutlity	Includes AE disutlity for altered-taste	Included	Included

AE: Adverse event; HR: Hazard ratio; ITC: Indirect treatment comparison; IVIg: Intravenous immunoglobulin; OS: Overall survival; PFS: Progression-free survival; QALYs: Quality-adjusted life years; 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's probabilistic base case is within the range normally considered a cost-effective use of NHS resources
- Scenarios presented in Part 2 will include alternative OS HRs

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme

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Other considerations- company real-world evidence analyses

Company DG consultation response

- Conducted an ITC using:
  - REALiTEC- teclistamab, n=113. Median age of 66 years
  - REALiTAL- talquetamab, n=93. Median age of 65 years
- Both retrospective, non-interventional studies deigned to evaluate real-world outcomes in people with triple-class exposed relapsed/refractory multiple myeloma
- Multivariable regression controlled for differences in baseline characteristics. Best approach for small sample sizes

Table: Summary of REALiTEC vs REALiTAL ITC OS HR

	OS HR (95% CI)	P-value
Observed HR (naïve, without multivariable regression) and no subsequent treatment adjustment	[redacted]	[redacted]
Observed HR including subsequent treatment adjustment	[redacted]	[redacted]
Adjusted HR (using multivariable regression) including subsequent treatment adjustment	[redacted]	[redacted]

CI: Confidence Interval; HR: Hazard Ratio; ITC: Indirect Treatment Comparison; OS: Overall Survival

Other considerations – EAG exploration of real-world evidence as per EAG report

Figure showing teclistamab reconstructed OS KM plots compared with the company KM plot

EAG critique

- Both teclistamab RWE studies (Riedhammer, 2024; Perrot, 2025) exhibit superior OS relative to the company KM curve
- Real-world use of talquetamab (Frenking,2025) suggests inferior OS and PFS to the company submission
- Understand data likely to represent different jurisdictions- Germany and France

NB: UK SACT data analysis completed but considered too immature for meaningful inference

Can real-world data be used to reduce uncertainty in the analysis?

See appendix SACT dataset summary and Evidence from recently published real-world studies from Europe

KM: Kaplan Meier OS: Overall survival; RWE: Real-world evidence

Other considerations – acceptable ICER (1)

ACM1 considerations

- Given the considerable uncertainties and based on the evidence and analysis, the committee considered an acceptable ICER would be around £20,000 per QALY gained

Company DG consultation response

- **Company considers a higher threshold is appropriate**
  - **Unmet need:** Talquetamab addresses a critical unmet need in TCE RRMM, offering an alternative target (GPRC5D) to BCMA therapies, with improved infection safety and potential survival gains
  - **Uncaptured benefits:** There are additional qualitative benefits of talquetamab, such as reduced caregiver burden, flexible dosing, lower infection-related anxiety, and enhanced patient and clinician choice, which are not reflected in the QALY-based economic evaluation

Has uncertainty in the evidence reduced? Are there uncaptured benefits?

ACM: Appraisal committee meeting; BCMA: B-cell maturation; DG: Draft guidance; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life years; RRMM: Relapsed or refractory multiple myeloma; TCE: Triple-class exposed

Other considerations

Equality considerations

- At ACM1 the committee considered that its recommendations do not restrict access to treatment for some people over others. So, the committee agreed that there were no potential equality issues in this evaluation.
- No equality issues have been raised during draft guidance consultation

Uncaptured benefits

- Are there any uncaptured benefits associated with talquetamab not included in the economic model?

- Are there any equality considerations to identify?
- Are all benefits and disadvantages of talquetamab captured adequately in the modelling?
- If not recommended for routine commissioning, would recommendations through managed access be feasible?

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**.

The company has not submitted a managed access proposal

Data source	What uncertainties could be resolved?
Trial-MonumenTAL-1	Final data cut- September 2024 used in this appraisal
SACT	For discussion

SACT: Systemic Anti-Cancer Therapy

Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ❑ ACM1 recap and DG consultation responses
- ❑ Clinical effectiveness evidence
- ❑ Modelling and cost effectiveness evidence
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations
- ✓ **Summary**

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Key issues and questions for committee

Clinical effectiveness issues

Talquetamab clinical effectiveness evidence

- Is clinical effectiveness of talquetamab from cohort C alone or larger pooled cohort A+C of MonumenTAL-1 more appropriate for decision making?
- Do the additional scenarios provided by the company using pooled cohort A+C reduce the uncertainty in the clinical evidence and ITC results?

ITC OS results: COVID-19 impact

- Is the company's OS HR censoring for deaths related to COVID-19 appropriate?
- Do either of company's approaches for censoring for deaths related to COVID-19 reduce the uncertainty in the ITC OS results?

ITC OS results: early separation of the OS curves

- Does the additional information provided by the company on early separation of talquetamab and teclistamab OS curves reduce the uncertainty in the ITC OS results?

ITC OS results: lack of correlation between PFS and OS

- Does the additional information provided by the company on the correlation between PFS and OS reduce the uncertainty in the ITC OS results?

Cost-effectiveness issues- largely resolved. Committee to confirm

Modelling OS, PFS and TTD

- Is the company's modelling using HR-based approach applied to uncalibrated Weibull distribution appropriate?

Subsequent treatments

- Do these analyses reduce uncertainty in the subsequent treatment adjustment?

HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies

Supplementary appendix

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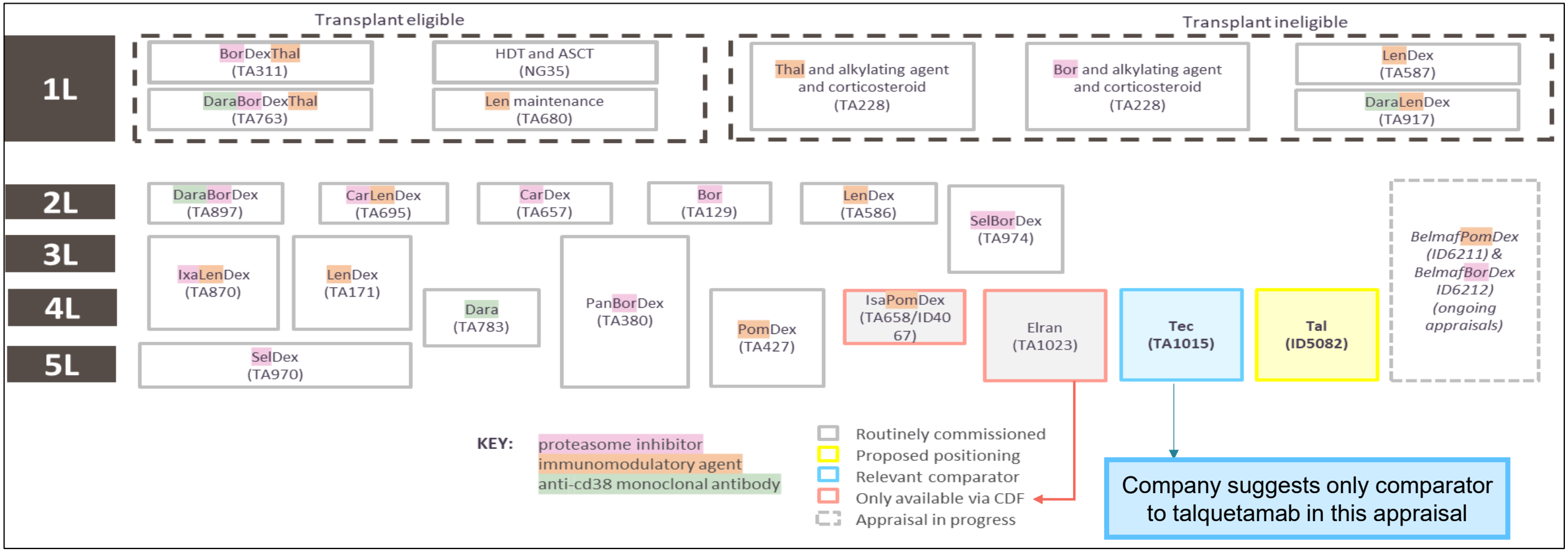
MM treatment pathway and proposed positioning of talquetamab



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1L/2L/3L/4L/5L: 1st/2nd/3rd/4th/5th line; ASCT: Autologous stem cell transplantation; Belmaf: Belantamab mafodotin; Bor: Bortezomib; BsAb: Bispecific antibody; Car: Carfilzomib; CD38: Cluster of differentiation 38; CDF: Cancer Drugs Fund; Dara: Daratumumab; Dex: Dexamethasone; Elran: Elranatamab; HDT: High dose therapy; Isa: Isatuximab; Ixa: Ixazomib; Len: Lenalidomide; MM: Multiple myeloma; NG: NICE guideline; Pan: Panobinostat: Pom: Pomalidomide; PomDex: Pomalidomide plus low dose dexamethasone; RRMM: Relapsed or refractory multiple myeloma: Sel: Selinexor; TA: Technical appraisal; Tal: Talquetamab; TCE: Triple-class exposed; TCR: T-cell redirecting; Tec: Teclistamab; Thal: Thalidomide

ACM1 conclusions- updates in company base case

Changes company have made post ACM1

Uncertainty	Changes made to company base case post DG consultation
ITC OS HR	Censored for deaths related to COVID-19
Modelling	Discounted from year 2 onward and exclude the half-cycle correction
Modelling OS, PFS and TTD	Aligning the extrapolations of teclistamab with the EAG- and committee-preferred approach of selecting the uncalibrated Weibull across OS, PFS and TTD
Subsequent treatments	Included costs and benefits of subsequent talquetamab and subsequent teclistamab following initial treatment
IVIg	• Used MonumenTAL-1 for proportion of IVIg use in the talquetamab arm and MajesTEC-1 for the teclistamab arm • Modelled for subsequent talquetamab and teclistamab treatments
AE disutilities	More explicit modelling of AE-disutilities and included the impact of altered taste and associated weight loss in the AE disutility for talquetamab

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ACM: Appraisal committee meeting; AE: Adverse event; DG: Draft guidance; HR: Hazard ratio; ITC: Indirect treatment comparisonIVIg: Intravenous immunoglobulin; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Consultation responses

J&J (company)

Key themes in company's consultation response to draft guidance:

- ITC analyses using pooled, unweighted data for cohort A+C in MonumenTAL-1
- COVID-19 censored OS ITC analyses
- Additional PFS2 analyses for cohort C in MonumenTAL-1
- Rationale for the OS benefit of talquetamab over teclistamab
- SACT data for talquetamab and teclistamab
- Impact of COVID-19 censored ITC analyses on economic results
- Scenario analyses with independent extrapolations for talquetamab and teclistamab without calibration to clinical expert estimates
- Alternate parametric distributions for the two-stage subsequent treatment adjustment
- Disutility associated with altered-taste
- Uncaptured benefits and ICER threshold

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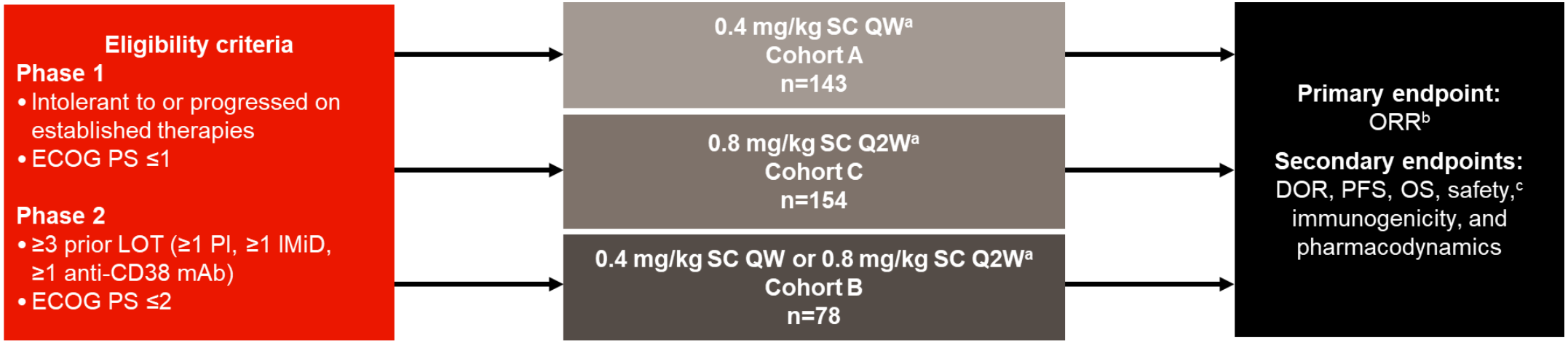
Key clinical trial: MonumenTAL-1 study design

Phase I/II, open-label, multicentre, international single-arm trial of talquetamab monotherapy for patients with TCE RRMM in 3 parts

Figure 6: MonumenTAL-1 study design



- Company considers that cohort C provides the most relevant evidence for talquetamab in this submission
  - Every 2 weeks dosing in cohort C is likely preferred in UK clinical practice compared with weekly dosing in cohort A due to greater convenience, fewer adverse events, and alignment with real-world evidence

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RRMM: Relapsed or refractory multiple myeloma; TCE: Triple-class exposed

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Key clinical effectiveness evidence: overview

MonumenTAL-1 and MajesTEC-1 study designs and outcomes

	MonumenTAL-1: all treated analysis set	MajesTEC-1: all treated analysis set (N=165)
Design	Phase I/II, open-label, single-arm, multicentre	Phase I/II, open-label, single-arm, multicentre
Population	Adults with RRMM: In phase 2, cohorts A and C were previously treated with IMiD, PI, and an anti-CD38 mAb	Adults with RRMM previously treated with an IMiD, PI and mAb
Intervention	Talquetamab	Teclistamab
Comparator	N/A	N/A
Duration	Median follow up: 31.2 months (cohort C), 38.18 (cohort A)	Median follow up: 30.4 months
Data cut-off	September 2024	August 2023
Primary outcome	Overall response rate	Overall response rate
Other outcomes	Include: DoR, response rates, OS, PFS, TTR, TTNT, MRD negativity rate, HRQoL and AEs	DoR, OS, PFS, MRD negativity rate, HRQoL and AEs
Locations	Belgium, France, Germany, Israel, Netherlands, Poland, Republic of Korea, Spain, US	**Phase I:** France, Netherlands, Spain, Sweden, US **Phase II:** UK, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, US, Canada, China

AEs: Adverse events; DoR: Duration of response; HRQoL: Health-related quality of life; IMiD: Immunomodulatory agent; mAb: Monoclonal antibody; MRD: Minimal residual disease; N/A: Not applicable; OS: Overall survival; PFS: Progression-free survival; PI: Proteasome inhibitor; RRMM: Relapsed or refractory multiple myeloma; TTNT: Time to next treatment; TTR: Time to response

Baseline characteristics: MonumenTAL-1 and MajesTEC-1

MonumenTAL-1 and MajesTEC-1 study baseline characteristics

		MonumenTAL-1 (Talquetamab):		MajesTEC-1: all treated analysis set (N=165)
		Cohort C (N=154)	Cohort A (N=143)	
Age, median (range), years		67.0 [redacted]	67.0 [redacted]	64.0 (33 to 84)
Male, n (%)		90 (58.4%)	78 (54.5%)	96 (58.2)
Time since diagnosis, median (range) years		6.28 [redacted]	6.69 [redacted]	6.0 (0.8 to 22.7)
Previous lines of treatment, median (range)		4.5 [redacted]	5 [redacted]	5 (2 to 14)
Extramedullary disease, n/N (%)		41 (26.6%)	33 (23.1%)	28/165 (17.0)
ISS, n/N (%)	I	68 (44.4%)	62 (43.4%)	85/162 (52.5)
	II	48 (31.4%)	53 (37.1%)	57/162 (35.2)
	III	37 (24.2%)	28 (19.6%)	20/162 (12.3)
	Unknown	NR	NR	NR
ECOG PS	0	58 (37.7%)	44 (30.8%)	55 (33.3)
	1	84 (54.5%)	86 (60.1%)	[redacted]
	2	12 (7.8%)	13 (9.1%)	NA
	3	NA	NA	[redacted]
High risk cytogenetic profile, n/N (%)		40 (30.1%)	41 (31.1%)	[redacted]
Prior ASCT, n (%)		[redacted]	[redacted]	[redacted]

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

Key results: MonumenTAL-1 and MajesTEC-1

MonumenTAL-1 and MajesTEC-1 study results

	MonumenTAL-1 (Talquetamab):		MajesTEC-1 (Teclistamab): All treated analysis set (N=165)
	Cohort C (N=154)	Cohort A (N=143)	
Median follow-up, months	31.2	38.18	30.4
ORR,% (95% CI)	69.5 [redacted]	74.1	63.0 [redacted]
≥CR, % (95% CI)	40.3 [redacted]	32.9%	46.1 [redacted]
Median PFS, months (95% CI)	11.2 (7.7, 14.6)	7.5 (5.7, 9.4)	11.4 [redacted]
Median OS, months (95% CI)	NE (NE, NE)	34.0 (25.6, NE)	22.2 [redacted]

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CI: Confidence interval; CR: Complete response; NE: Not estimable; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival

ITC results at ACM1 – Overall survival

OS K–M curves for talquetamab and ATT weighted teclistamab, following subsequent treatment adjustment to reflect current UK clinical practice (**Company's base case**)

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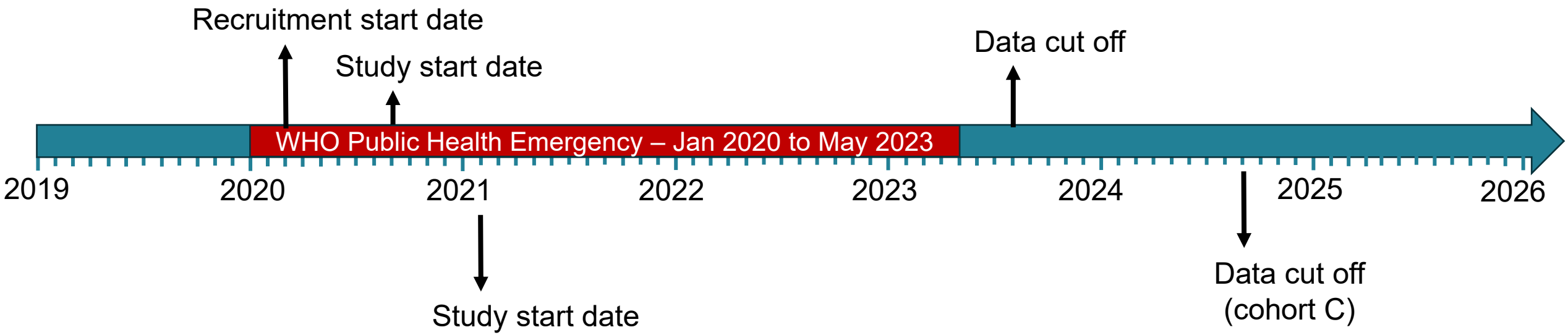
ATT: Average treatment effect for the treated; CI: Confidence interval; HR: Hazard ratio; ITC: Indirect treatment comparison; K–M: Kaplan–Meier; OS: Overall survival

Clinical trial evidence in relation to COVID-19 timeline

MajesTEC-1 (teclistamab) – Median follow up 30.4 months



MonumenTAL-1 (talquetamab) – Median follow up 31.2 months

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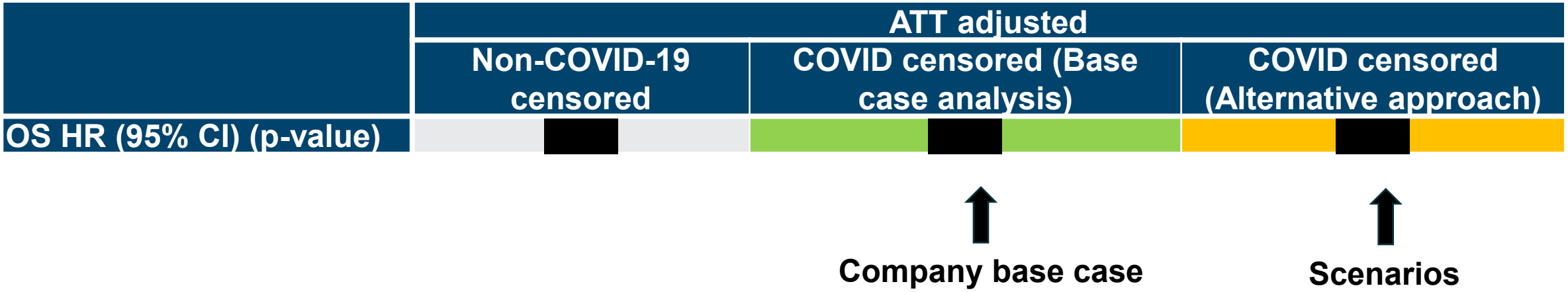
ITC: Indirect treatment comparison; WHO: World Health Organisation

ITC OS results: COVID-19 impact

Comparison of COVID-related death censored OS between talquetamab (pooled 10:90 weighted cohort A+C) and teclistamab (ATT-adjusted)



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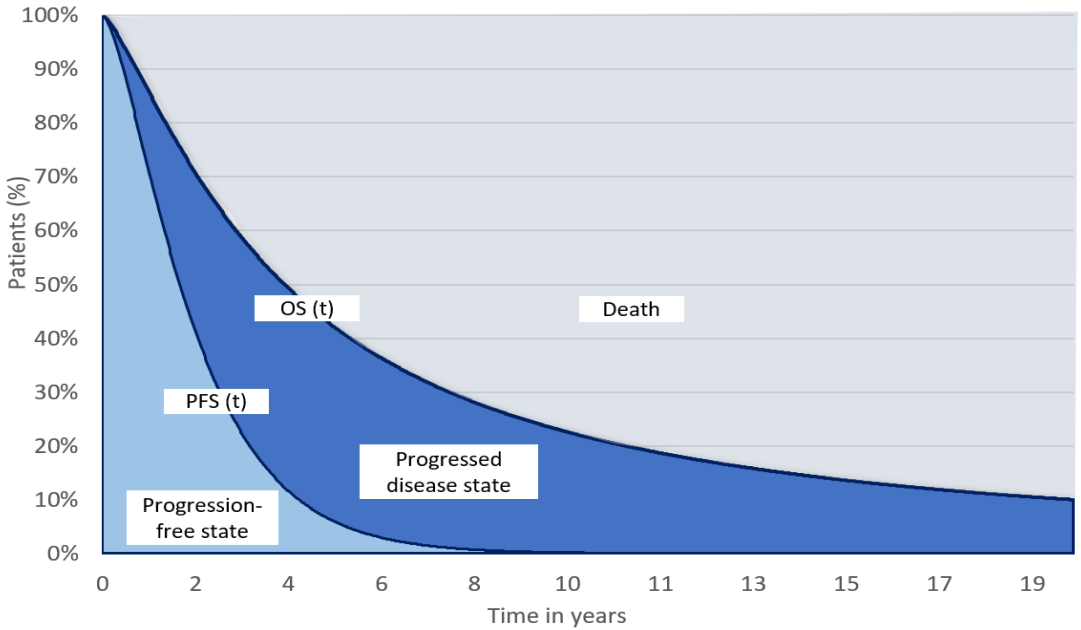
NICE

ATT: Average treatment effect for the treated; HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival

Company's model overview

- Partitioned survival model
- Life-time horizon of 40 years using 1-week cycles
- State occupancy informed by OS and PFS extrapolations from MajesTEC-1 for teclistamab and applying HRs from ITC to these extrapolations for cohort C of MonumenTAL-1 to derive long-term extrapolations for talquetamab

Figure 4: Model structure



Treatment affects QALYs by:

- Changing the OS
- Changing the PFS

Treatment affects costs by:

- Drug acquisition, drug administration and subsequent treatment costs
- Health state management costs
- Adverse event costs and end-of-life care costs

Assumptions with greatest effect on cost-effectiveness results:

- Talquetamab versus teclistamab OS HR
- Talquetamab versus teclistamab TTD HR
- Equal use of intravenous immunoglobulin (IVIg) treatment between both arms

HR: Hazard ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; QALYs; Quality-adjusted life years; TTD: Time to treatment discontinuation

Modelling OS, PFS and TTD at ACM1

EAG generated lognormal model for talquetamab OS together with lognormal models fit to Kaplan–Meier plot for talquetamab OS

- To make the lognormal model plausible, the company adjusted and forced the model to comply with clinical prediction
- Two adjusted lognormal models are represented by blue and brown dashed lines ➔ The EAG interpret these as an adjustment to 15 years with a further adjustment to the 40-year horizon. Only after two adjustments is the lognormal model plausible

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ACM: Appraisal committee meeting; K–M : Kaplan–Meier; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Modelling OS, PFS and TTD - company scenarios

Company DG consultation response

- Scenarios- all post subsequent treatment adjustment:
  - Scenario 6- Teclistamab OS, PFS and TTD- Weibull, Talquetamab (cohort C) OS- Gamma, PFS and TTD- lognormal
  - Scenario 7- Teclistamab OS, PFS and TTD- Weibull, Talquetamab (cohort C) OS- Weibull, PFS and TTD- lognormal
  - Scenario 8- Teclistamab OS, PFS and TTD- Weibull, Talquetamab (10:90 weighted cohort A+C) OS- Gamma, PFS and TTD- lognormal
  - Scenario 9- Teclistamab OS, PFS and TTD- Weibull, Talquetamab (10:90 weighted cohort A+C) OS- Weibull, PFS and TTD- lognormal

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ATT: Average treatment effect for the treated; DG: Draft guidance; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; ITC: Indirect treatment comparison; OS: Overall survival; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Other considerations – SACT dataset

Background

- Provides demographic and OS data for adults receiving teclistamab (n=139) or talquetamab (n=39) in the NHS with RRMM at 4L+
- Relevancy issue- TA1015 Teclistamab became available in the NHS November 2024. People captured in SACT accessing teclistamab and talquetemab through compassionate use. Different characteristics.

Company DG consultation response

- SACT data are inappropriate for decision-making as per NICE's real-world evidence framework
- ITCs using robust trial data and adjustment for key prognostic factors more appropriate for evaluating talquetamab's effectiveness
- ITC using REALiTAL and REALiTEC data, adjusted for baseline differences, is more robust and supports talquetamab's survival benefit and provides supplementary real-world evidence to contextualise the updated base case

EAG critique

- Limited meaningful inference
- Exploratory comparison generated OS HR=0.85 in favour of talquetamab. More in line with regression analysis by Etekal et al. of relapsed refractory MM.
- Real world studies useful and likely un-associated with problems from the COVID pandemic. Included in EAG report. Teclistamab: Riedhammer, 2024; Perrot, 2025 and talquetemab: Frenking, 2025.

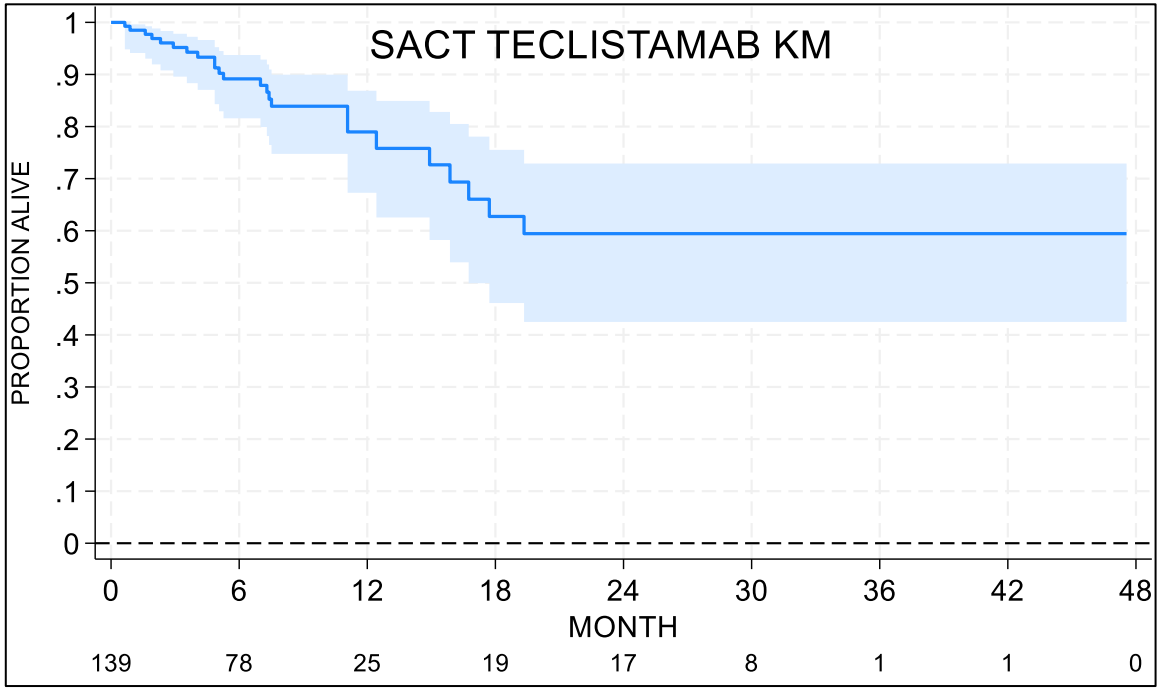
DG: Draft guidance; ITC: Indirect treatment comparison; OS: Overall survival; RRMM: Relapsed or refractory multiple myeloma; SACT: Systemic Anti-Cancer Therapy

Other considerations – SACT dataset summary

Table: summary of teclistamab and talquetamab use in SACT dataset

Teclistamab		
Characteristic	Female N = 58[1]	Male N = 81[1]
Age at treatment start	65, (9) : 66 (59, 73)	68, (9) : 69 (59, 75)
Median survival	Not reached	
Restricted mean survival (over the whole curve)	32.95 months	
Talquetamab		
Characteristic	Female N = 16[1]	Male N = 23[1]
Age at treatment start	60, (11) : 61 (53, 69	63, (7) : 64 (58, 68)
Median survival	Not reached	
Restricted mean survival (over the whole curve)	18.19 months	
[1]Mean, (SD) : Median (Q1, Q3)		

Figure: SACT OS of UK teclistamab treated patients (n=139); KM analysis



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NICE

KM: Kaplan Meier; OS: Overall Survival; SACT: Systemic Anti-Cancer Therapy; SD: Standard deviation

Evidence from recently published real-world studies from Europe

[redacted]

[redacted]

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NICE

CI: Confidence interval; HR: Hazard ratio; ITC: Indirect treatment comparison; K–M: Kaplan–Meier; OS: Overall survival

Decision making framework (1/2)

Question for committee	Tech team consideration
What are committee's preferred assumptions?	
• Is clinical effectiveness of talquetamab from cohort C alone or larger pooled cohort A+C of MonumenTAL-1 more appropriate for decision making? • Do the additional scenarios provided by the company using pooled cohort A+C reduce the uncertainty in the clinical evidence and ITC results?	
• Is the company's OS HR censoring for deaths related to COVID-19 appropriate? • Do either of company's approaches for censoring for deaths related to COVID-19 reduce the uncertainty in the ITC OS results?	
• Does the additional information provided by the company on early separation of talquetamab and teclistamab OS curves reduce the uncertainty in the ITC OS results?	
• Does the additional information provided by the company on the correlation between PFS and OS reduce the uncertainty in the ITC OS results?	
• Is the company's modelling using HR-based approach applied to uncalibrated Weibull distribution appropriate?	
• Do these analyses reduce uncertainty in the subsequent treatment adjustment?	
What is the committee's preferred ICER threshold?	
What is the committee's preferred ICER?	
Is the ICER below the preferred ICER threshold?	

HR: Hazard ratio; ITC: Indirect treatment comparison; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PFS: Progression-free survival

Decision making framework (2/2)

Question for committee	Tech team consideration
What are committee's preferred assumptions?	
If yes, can this be recommended for routine commissioning (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold)?	
If not, could the key uncertainties be sufficiently resolved during a period of managed access? If so:	
• Has the company made a managed access proposal? Is this considered feasible?	
• Are any updates or amendments required to the managed access proposal?	
• Has the committee answered the questions in NICE's feasibility assessment?	
• What is committee's preferred threshold for managed access?	
• Which ICERs/assumptions represent committee's lower/upper end of uncertainty?	
What, if any, are the key remaining uncertainties?	
• Equality considerations	

ICERs: Incremental cost effectiveness ratios