Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Johnson & Johnson Innovative Medicine**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. UK Myeloma Society (written by clinical experts: Dr Sarah Lawless – nominated by UK Myeloma Society; and Dr Neil Rabin – nominated by Johnson and Johnson Innovative Medicine)
   b. Myeloma UK (written by patient expert: Caroline Donoghue – nominated by Myeloma UK)

3. **SACT report:**
   a. National Disease Registration Service SACT report
   b. Comments on the SACT report from Johnson & Johnson Innovative Medicine

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jonhson and Johnson Innovative Medicine

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Esther Cheah

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive Summary	The Company extends their appreciation to the Committee for their time and consideration during the appraisal Committee meeting (ACM) and are grateful for the opportunity to provide comments on the Draft Guidance Document (DGD) to address the Committee's key areas of uncertainty. The Company welcomes the Committee's comments in the DGD highlighting the substantial impact multiple myeloma (MM) has on patient's survival and quality of life, and the unmet need for more effective treatments for patients with MM who have had several treatments. In light of these comments, the Company is disappointed by the draft guidance which does not recommend talquetamab for the treatment of adults with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). Talquetamab addresses the significant unmet needs in this disease area, representing a novel treatment option that would be highly valued by both patients and clinicians.

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	The Company acknowledges the discussions at the ACM and the potential uncertainties related to the evidence base noted by the Committee. To address these uncertainties, the Company has: (1) Revised the Company base case to incorporate the Committee's preferred assumptions, as confirmed in the DGD (see Appendix 1), and (2) Provided additional analyses as part of this response, including those explicitly requested by the Committee in the DGD, further details of which are outlined below: ***Comment 1: Indirect treatment comparison (ITC) analyses using pooled, unweighted data for Cohort A+C in MonumenTAL-1*** As discussed further in Comment 1, Cohort A (weekly dosing) is less relevant than Cohort C (biweekly dosing) for decision making. Clinical feedback received by the Company and stated in ACM1 (DGD, page 7) confirmed that the vast majority (90%) of patients in UK clinical practice will receive the biweekly (Q2W) regimen with 10% receiving the weekly (QW) regimen, owing to its increased convenience (aligning with patient preference and reduced healthcare resource requirements) and more favourable safety profile.[1] In the DGD (Page 7), the Committee also stated that they were *"unclear why the clinical efficacy would differ markedly between these 2 dosing regimens"* and requested pooled unweighted data for Cohort A (QW) and C (Q2W) in MonumenTAL-1. The Company would like to clarify that more patients in Cohort A versus C required dose modifications and/or reductions, ultimately meaning that patients in Cohort C were on treatment for longer than Cohort A, allowing patients in Cohort C to derive additional treatment benefit. Furthermore, evidence from MonumenTAL-1 demonstrates that the reduced frequency of dosing of talquetamab in Cohort C resulted in improved immune fitness and T cell recovery in patients, again enabling them to remain on treatment and therefore derive benefit from treatment for longer versus those in Cohort A.[2, 3] As requested by the Committee in the DGD, ITC analyses using pooled, unweighted data from Cohort A+C of MonumenTAL-1 have been provided in Comment 1. The results are consistent with the Cohort C ITC provided in the Company submission (Section 2.10), demonstrating that talquetamab significantly extends overall survival (OS) when compared to teclistamab (unweighted Cohort A+C OS hazard ratio [HR]: [redacted] [95% confidence interval {CI}: [redacted], p[redacted]; Cohort C OS HR: [redacted][95% CI: [redacted], p[redacted]), alongside having comparable progression-free survival (PFS) and time to treatment discontinuation (TTD). Whilst pooled Cohort A+C ITC results have been provided, the Company would like to highlight that these data assume approximately equal weighting of Cohort A and C (due to the relative cohort sizes in the trial); this is not representative of the anticipated use of

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	talquetamab in UK clinical practice based on feedback received from clinical experts by the Company and during the ACM that 90% of patients would receive the biweekly regimen. As such, the results of this analysis have not been included in the economic model as they are not informative regarding the costs and benefits likely to be seen in clinical practice. The Company notes the Committee expressly considered '*it may be appropriate to model resource use according to 10% of dosing regimens being once weekly and 90% being once every two weeks*' (DGD, page 7). Given the inherent link between efficacy and dosing regimen, the Company has provided the 10:90 weighted A+C as a scenario analysis in the economic model, whereby both resource use and efficacy data have been weighted accordingly, the results of which are presented in Appendix 2. Results of this scenario analysis are highly consistent with that of the base case analysis. The Company however wish to emphasise that since Cohort A is associated with worsened efficacy and a less favourable safety profile compared to Cohort C, there is no clinical reason for the weekly regimen to be chosen over the biweekly regimen in UK clinical practice. As a result, the analyses using the pooled, 10:90 weighted data from Cohort A+C from MonumenTAL-1 represent a conservative assumption. ***Comment 2a: COVID-19 censored OS ITC analyses*** The Company has also performed additional ITC analyses for Cohort C in MonumenTAL-1 to address uncertainty in the ITC HR for OS, including a survival analysis censoring for deaths related to COVID-19, as requested by the Committee in the DGD. The results of these analyses, in which deaths due to COVID-19 in the MonumenTAL-1 and MajesTEC-1 trials were censored, show consistent findings with the uncensored ITC. A significant OS benefit in favour of talquetamab continued to be observed, with a similar magnitude of benefit to the non-COVID censored analyses (Comment 2a). In the revised Company base-case, all patients with COVID-related deaths who did not progress while on treatment and at least achieved complete response (CR+) as the best response before death were censored. This approach reduces the potential for selection bias by only censoring those patients with the highest potential for long-term survival, if they had not died due to COVID-19. This analysis produced a HR of [redacted] (95% CI:[redacted]; p=[redacted]. In comparison, the analysis whereby COVID deaths were not censored produced a HR of [redacted] (95% CI: [redacted]); [redacted] (subsequent treatment-adjusted ITC results which included subsequent talquetamab and teclistamab). ***Comment 4: Impact of COVID-19 censored ITC analyses on economic results***

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The impact of using the OS HRs from these COVID-censored ITC analyses have been explored in scenario analyses in the model (Comment 4), which show that the ICER is robust to censoring for patients who died due to COVID-19.

Comment 2b: PFS2 analyses for Cohort C in MonumenTAL-1

To further characterise the benefit of talquetamab over teclistamab, the Company has also provided new analyses of PFS2 (defined as the time between the study treatment start date and date of event [defined as progressive disease as assessed by investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first]; Comment 2b). In these analyses, talquetamab was associated with a significant improvement in PFS2 compared to teclistamab (HR: [redacted] [95% CI: [redacted]]; p=[redacted]). These findings support the observed OS benefit of talquetamab over teclistamab and the rationale that patients receiving talquetamab experience less severe T cell exhaustion than patients receiving teclistamab (as detailed below),and so are more likely to derive additional benefits from subsequent treatment.

Comment 2c: Rationale for the OS benefit of talquetamab over teclistamab

All ITC analyses, before and after COVID-19 censoring, and additional PFS2 analyses clearly demonstrate the significant OS benefit in favour of talquetamab. The reasons for this OS benefit are multi-faceted [redacted].

As supported by literature, by targeting GPRC5D, talquetamab leads to **less suppression of humoral immunity** than BCMA-targeting drugs, since BCMA is found on some mature B cells and plasma cells essential for the humoral immune response.[4-6] Subsequently, patients treated with talquetamab have a lower risk of severe infections and hypogammaglobulinemia compared those receiving teclistamab.[6, 7] [redacted][8-10]

Furthermore, as noted by the Company during the ACM, following weekly administrations of BCMA-targeting BsAbs such as teclistamab, patients' T cells may not respond effectively to further T cell-redirecting therapies as they experience T cell exhaustion.[11, 12] Meanwhile, by receiving talquetamab every other week, patients T cells are able to reinvigorate and recover.[3] Over time, the T cell function is preserved from exhaustion and can continue to sustain survival gains with subsequent therapies.

The results of the PFS2 analyses in Comment 2b further support that patients are able to derive additional benefits from subsequent treatments following treatment with talquetamab compared to following treatment with teclistamab. This may be explained by the increased

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	immune fitness (and less severe T cell exhaustion) of patients following disease progression on talquetamab compared to the immune fitness of patients following progression with teclistamab. Finally, the Company has also provided additional data in Comment 2c to address uncertainty around the early separation in OS Kaplan-Meier (KM) curves for talquetamab and teclistamab. There were more than [redacted] as many deaths in MajesTEC-1 compared to MonumenTAL-1 during the first three months ([redacted]% compared to [redacted]%, respectively) and in both treatment arms, the majority of deaths were caused by disease progression ([redacted]% in MajesTEC-1 compared to [redacted]% in MonumenTAL-1, respectively).[7, 13] A plausible explanation is the significant overall response rate (ORR) benefit of talquetamab over teclistamab in the ITC performed in the Company submission (Section 2.10.5). The Company notes that the early drop in OS curve for teclistamab is an effect observed consistently across other BCMA BsAbs.[14, 15] ***Comment 3: SACT data for talquetamab and teclistamab*** NICE provided SACT data for teclistamab and talqutamab on 19th September 2025, just 4 working days before the deadline for this draft guidance response. As such and as agreed with NICE, the Company response considering these SACT data will be provided in a separate document. ***Comment 5: Scenario analyses with independent extrapolations for talquetamab and teclistamab without calibration to clinical expert estimates*** The Company has provided scenario analyses with independent extrapolations fit to the talquetamab and teclistamab data and without calibration to clinical expert estimates in line with the Committee's request in the DGD (Comment 5). While these scenarios have been provided, the Company maintain that the HR modelling approach adopted in the Company submission (see Section 3.3) is more appropriate than independently fit curves for the below reasons: 1. **PH assumption clearly holds:** The proportional hazards (PH) assumption clearly holds between talquetamab and teclistamab. As such, the HR approach is the most appropriate methodology for generating long-term survival estimates for talquetamab, in line with NICE technical support document (TSD)14.[16] 2. **EAG are in agreement with the Company that the PH-based approach is justified:** The EAG noted in their critique (Section 3.4.6.1 of the EAG report) that they agree a PH-based approach is justified for the comparison of talquetamab and teclistamab as the PH assumption is not violated.

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	3. **HR approach is associated with significantly less uncertainty than the independent modelling approach and is grounded on the best available evidence:** The HR approach incorporates the ITC results directly, ensuring the clinical plausibility of the model and accurately reflects the treatment effect. Moreover, the robustness of the ITC cannot be underestimated wherein the Company had access to the IPD of both trials and ensured relevant patient baseline characteristics were well-matched. This approach provides long-term extrapolations grounded in observed data. Conversely, the independent modelling approach relies on subjective assumptions and therefore is associated with increased uncertainty. As such, the HR approach is associated with significantly less uncertainty than the independent modelling approach and is grounded on the best available evidence. The results of the scenario analyses exploring independent extrapolations of the talquetamab and teclistamab data are presented in Comment 5 and are broadly consistent with the revised base case analysis, thereby minimising uncertainty associated with the method adopted by the Company in the base case analysis. ***Comment 6: Additional details on subsequent treatment adjustment methods*** As requested by the Committee in the DGD, the Company has provided a more detailed explanation of the overall methods used to adjust for subsequent treatments not available in UK clinical practice, alongside ITC scenario analyses in which alternative parametric distributions to Weibull are used to adjust for subsequent treatments. The results of these analyses are highly consistent with those using the Weibull distribution, thereby demonstrating that the Company's base case ITC result is robust to uncertainty regarding the distribution selected for subsequent treatment adjustment. **Revised Company base case: the Company has revised their base case to incorporate Committee's preferred assumptions** Alongside the Comments above, the Company has also provided a revised base case which: • Incorporates all of the Committee's preferred assumptions as outlined in the DGD (page 19)., • Incorporates the EAG's preferred assumption of using the Weibull distribution to extrapolate the teclistamab OS, PFS and TTD curves. • Includes an updated HR generated from the COVID-censoring analyses detailed in Comment 2a.

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- Includes the disutilities associated with dysgeusia as an adverse event (AE; as detailed in Comment 7), in recognition of the health-related quality of life (HRQoL) impact that dysgeusia may have on patients receiving talquetamab

A complete list of the changes made to the base case cost-effectiveness analyses including the cumulative changes to the Company cost-effectiveness estimates, including the Committee-preferred assumptions, are presented in Table 11, with the revised base case results presented in Table 12 (probabilistic results) and Table 13 (deterministic results).

Following inclusion of all Committee-preferred assumptions, talquetamab represents a cost-effective use of the NHS resources compared with teclistamab when considering an appropriate willingness-to-pay (WTP) threshold of £30,000/QALY (see Comment 8).

A summary of the scenario analyses conducted by the Company as part of this response is also provided in Table 14 (Appendix 2).

The company intends to submit a revised patient access scheme (PAS) discount for talquetamab of [redacted]%, resulting in a PAS price of £[redacted] and £[redacted] for the 3 mg/1.5 mL and 40 mg/1 mL doses of talquetamab, respectively. This revised PAS has been included in the updated model results and scenario analyses discussed throughout this response document.

Finally, three factual inaccuracies identified within the DGD (p9, p10 and p14) are detailed in Appendix 3.

Summary

The Company has provided a comprehensive set of additional analyses as part of this response. Prior to the second Committee meeting, the Company has revised its PAS discount for talquetamab and base case economic analyses to include all of the Committee's preferred assumptions, thereby addressing and reducing uncertainty in the clinical and cost-effectiveness evidence base for decision-making.

Furthermore, whilst the Committee has clearly acknowledged the unmet need for more efficacious treatments in MM (DGD, page 5), the Company is extremely disappointed that this unmet need is not reflected in the willingness-to-pay threshold set for talquetamab. Despite the step-change in the treatment pathway with the advent of teclistamab, TCE RRMM remains a terminal, end of life illness, with a median OS of less than 24 months.[17] Alternative treatment options with novel targets, such as talquetamab are therefore desperately needed to enhance patients life expectancy and provide patient and clinicians choice; a fundamental aspect of NHS care.[18, 19]

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	There are also several benefits of talquetamab that have not been captured in the economic analyses (as discussed in Section 3.13 of the Company submission) which the Committee has not taken into account. The value of hope, reductions in anxiety associated with the introduction of talquetamab and the benefits of its novel target are not accounted for in the modelling approach. As discussed in Comment 8, in light of the high unmet need in the TCE RRMM setting, uncaptured benefits in the economic analysis and the additional analyses that repeatedly demonstrate the magnitude of OS benefit for talquetamab versus teclistamab, a willingness-to-pay threshold of £20,000 per QALY gained is inappropriate and should be reconsidered.
Comment 1	**ITC analyses using the pooled, unweighted MonumenTAL-1 A+C Cohorts have been presented as requested by the Committee. The results of these analyses are consistent with the Company base case ITC results using Cohort C.** The Company acknowledges the Committee's statement that limited clinical effectiveness evidence was provided from Cohort A of MonumenTAL-1 in the CS (DGD, p18). However, as discussed in the CS (Section 2.3.1), the Company maintain that Cohort C (biweekly regimen) provides the most relevant evidence for talquetamab in UK clinical practice and decision making. Clinical feedback received by the Company and during the ACM clearly established that most UK patients will receive the biweekly (Q2W) regimen, owing to its increased convenience (aligning with patient preference and reduced healthcare resource requirements) and improved safety profile.[1] In line with clinical advice, the Company had provided an ITC scenario of talquetamab (Cohort A+C, weighted as per the 10:90 split validated by clinical experts) and teclistamab. The PFS results for this comparison are presented in Section 2.10.6, Table 37 of the Company submission. In line with the Committee's preferred assumptions of adding subsequent talquetamab after teclistamab, the Company has now provided the updated results of the aforementioned comparison presented in Figure 12 (Appendix 4) of this response. The results are highly consistent with the ITC using just Cohort C (OS HR [weighted Cohort A+C]: [redacted]; OS HR [Cohort C]: [redacted]). The clinical effectiveness results of Cohort A in MonumenTAL-1 were also provided in Appendix L.2 of the Company submission. As requested by the Committee, an additional ITC sensitivity analysis was performed comparing talquetamab with teclistamab (using pooled, unweighted data from Cohorts A+C in MonumenTAL-1 and including the use of subsequent talquetamab and teclistamab). As this analysis approximately assumes an equal split of patients receiving the QW (48.1%) and Q2W (51.9%) dosing regimens (reflecting the relative cohort sizes in MonumenTAL-1), this analysis is not reflective of the anticipated use of talquetamab in UK clinical practice. As

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such, these data do not reflect the costs and benefits likely to be seen in clinical practice and have not been included in the economic model. A summary of the results from this comparison is presented below with further details presented in Appendix 4.

Results

PFS, OS and TTD for talquetamab, including both pooled, unweighted A+C data as well as pooled, 10:90 weighted Cohort A+C data relative to teclistamab after ATT-adjustment are presented in Table 1. The KM curves for these comparisons are also provided in Appendix 4 (Figure 15, Figure 16, and Figure 17 for PFS, OS and TTD, respectively). When considering the unweighted Cohort A+C data, treatment with talquetamab resulted in comparable PFS and TTD compared to treatment with teclistamab (PFS HR [redacted] [95% CI [redacted]] p=[redacted]; TTD HR [redacted] [95% CI [redacted]] p=[redacted]). However, the unweighted Cohort A+C talquetamab data shows a significant improvement in OS compared to teclistamab (HR: [redacted][95% CI: [redacted]], p[redacted]). The magnitude of OS benefit is slightly reduced but remains largely aligned with both the 10:90 weighted Cohort A+C ITC results and the Cohort C ITC results (Table 1; weighted Cohort A+C HR: [redacted][95% CI: [redacted]], p[redacted] Cohort C HR: [redacted][95% CI: [redacted]], p=[redacted]).

Table 1. 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)

Comparison	Naïve (pooled, unweighted Cohort A+C)	Adjusted		
		ATT (Cohort C)	ATT (pooled, unweighted Cohort A+C)	ATT (pooled, 10:90 weighted Cohort A+C)
PFS				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
OS[a]				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
TTD				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

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Footnote: [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.
Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.

In the DGD, the Committee noted it was unclear why the *"clinical efficacy would differ markedly between the two regimens*". The Company would like to clarify the following points in relation to the differences in efficacy between Cohort A and C, as supported by the results of MonumenTAL-1:[7]

- **Differences in treatment duration:** There are several factors which point towards differences in dose reduction/modification and patients remaining on treatment for longer in Cohort C compared to Cohort A, therefore allowing patients in Cohort C to derive additional benefit from treatment:
  - More patients in Cohort A versus Cohort C required a dose reduction ([redacted]% vs [redacted]%).[7]
  - More patients in Cohort A versus Cohort C required a dose modification (dose reduction, dose skip or dose delay) due to a TEAE (71.3% vs 60.4%).[7]
  - The median time on treatment was [redacted] months in Cohort A and [redacted] months in Cohort C.[7]
  - Talquetamab was administered for ≥6 months in [redacted]% and [redacted]%, ≥9 months in [redacted]% and [redacted]%, and ≥12 months in [redacted]% and [redacted]% in Cohorts A and C respectively.[7]
  - The median number of cycles was [redacted] and [redacted], and patients received at least 24 cycles for [redacted]% and [redacted]% of Cohorts A and C, respectively.[7]
- **Differences in T cell exhaustion:** Patients in Cohort C are able to remain on treatment for longer and thus derive benefit from treatment for longer because T cell exhaustion is reduced compared to Cohort A. Vishwamitra, *et al.* 2023 highlighted that expression markers of T cell exhaustion were observed more readily in non-responders in Cohort A of MonumenTAL-1, compared with Cohort C, suggesting the biweekly dosing regimen delays T cell exhaustion.[3] This is further supported by evidence from MonumenTAL-1 showing that reduced dosing frequency of talquetamab (i.e., Q2W compared to QW) resulted in improved immune fitness and T cell recovery in patients with TCE RRMM.[2]

Summary

As requested by the Committee, the Company has provided pooled, unweighted Cohort

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	A+C ITC analyses, the results of which are aligned with both the 10:90 weighted Cohort A+C and the Cohort C ITC results (Table 1). However, the Company maintains that if Cohort A data are to be considered, the pooled, 10:90 weighted Cohort A+C data is more appropriate to inform decision making. This is in line with feedback received from clinical experts, both pre-submission and during ACM1 that only 10% of patients are anticipated to receive the talquetamab weekly regimen (i.e., Cohort A) in clinical practice.[20] Furthermore, since Cohort A is associated with worsened efficacy and a less favourable safety profile compared to Cohort C, there is no clinical reason for the weekly regimen to be chosen over the biweekly regimen in UK clinical practice. As a result, the analyses using the pooled, 10:90 weighted data from Cohort A+C from MonumenTAL-1 are conservative. Together, the available evidence indicates that the pooled unweighted Cohorts A+C ITC analyses results have limited relevance for UK decision making; therefore, these ITC results have not been incorporated in the economic model. The Company notes the Committee expressly considered '*it may be appropriate to model resource use according to 10% of dosing regimens being once weekly and 90% being once every two weeks*', in line with the estimate from a clinical expert during the ACM (DGD, page 7). Given the inherent link between efficacy and dosing regimen, the Company has provided the 10:90 weighted A+C as a scenario analysis whereby both resource use and efficacy data have been weighted accordingly, the results of which are presented in Appendix 2. Results of this scenario analysis are highly consistent with that of the base case analysis.
Comment 2a	**COVID-censored ITC analyses are highly consistent with the uncensored ITC results, demonstrating that the OS benefit for talquetamab versus teclistamab cannot be solely attributed to differing numbers of deaths due to COVID-19 in the MonumenTAL-1 and MajesTEC-1 trials** The Committee noted that the MonumenTAL-1 and MajesTEC-1 trials were conducted at different timepoints during the COVID-19 pandemic, and the Committee queried whether this accounted for some of the OS benefit observed with talquetamab compared to teclistamab (DGD, p11). To address the uncertainty surrounding the impact of COVID-19 on the results and the OS benefit in favour of talquetamab, the Company has provided additional sensitivity analyses that censor deaths due to COVID-19 in MonumenTAL-1 and MajesTEC-1, as requested by the Committee, and incorporated the HRs generated from these analyses in the revised base case (see below) or the scenario analyses. Overall, [redacted] COVID-related deaths were reported in Cohort C of MonumenTAL-1, compared to [redacted] COVID-related deaths in MajesTEC-1. In the base case censoring analysis, all patients

with COVID-related deaths who did not progress while on treatment and had a CR+ as their best response before death were censored. In this approach, only patients with a favourable prognosis prior to death were censored. Patients who experienced disease progression, or who did not achieve a complete response to treatment were not censored, as these patients were considered likely to have a poor prognosis independently of COVID-19. This approach reduces the potential for selection bias by only censoring those patients with the highest potential for long-term survival, if they had not died due to COVID-19 and was incorporated in the revised base case of the economic model (Appendix 1).

An alternative approach, in which all [redacted] patients with COVID-related death were censored, was also explored. [redacted]. In light of these considerations, this approach was excluded from the revised base case but explored separately as a scenario to evaluate its impact on the ICER.

Two additional scenario analyses have been conducted using the same COVID-19 censoring rules using the pooled 10:90 weighted Cohort A+C cohort.

Table 2 below summarises the number of patients censored in each treatment arm in the analyses:

Table 2. Number of patients censored due to death caused by COVID-19 in the ITC analyses

Approach	Talquetamab (Cohort C)	Talquetamab (weighted 10:90 Cohort A+C)	Teclistamab[a]
Base case approach; censor all patients with COVID-related deaths who did not progress while on treatment and had a complete response or better (CR+) as the best response before death[b]	[redacted]	[redacted]	[redacted]
Alternative approach; censoring all patients with COVID-related deaths	[redacted]	[redacted]	[redacted]

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Footnotes: [a] [redacted] 12 [redacted].

[b] Although this approach only censored patients who achieved at least CR, patients who achieve at least VGPR are also likely to have favourable long-term survival.
Abbreviations: CR+; complete response or better; ITC: indirect treatment comparison.

A summary of the results from these COVID-censored ITC analyses are presented below with full details presented in Appendix 5.

Results: Cohort C

The HR for OS after censoring for patients with COVID-related deaths using both approaches for the ATT-adjusted MonumenTAL-1 Cohort C analyses are presented in Table 3.

- Base case: censor all patients with COVID-related deaths who did not progress while on treatment and had a CR+ as the best response before death
- Alternative: censoring all patients with COVID-related deaths

Table 3. Comparison of COVID-related death censored OS between talquetamab (Cohort C) and teclistamab (ATT-adjusted)

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

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

The consistently strong OS benefit of talquetamab over teclistamab across the various analyses (base case COVID-censored analysis HR: [redacted]; alternative COVID-censored approach HR: [redacted]; non-COVID-19 censored HR: [redacted]) clearly shows **evidence of an OS benefit after accounting for COVID-19 impact**. The rationale for the OS benefit is discussed further in Comment 2c.

For completeness, and to further address any remaining uncertainty highlighted by the Committee in the DGD, the Company has provided additional COVID-censored ITC analyses, using the weighted 10:90 Cohort A+C data to inform the efficacy of talquetamab.

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The results for these analyses, with COVID-censoring using both censoring approaches are summarised below with additional KM curves presented in Appendix 5.

Results: 10:90 weighted, Cohort A+C

The HR for OS for the 10:90 weighted, Cohort A+C population before and after censoring for patients with COVID-related deaths (base case approach and alternative approach), for the ATT-adjusted analyses, are presented in Table 4 below.

Table 4. Comparison of COVID-related death censored OS between talquetamab (pooled 10:90 weighted Cohort A+C) and teclistamab (ATT-adjusted)
<table>
<tr><th></th><th colspan="3">ATT-adjusted</th></tr>
<tr><th>Comparison</th><th>Non-COVID-19 censored</th><th>COVID censored (Base case analysis)</th><th>COVID censored (Alternative approach)</th></tr>
<tr><td>OS HR (95% CI)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>p-value</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; OS: overall survival.

These results highlight the consistency of the significant OS benefit in favour of talquetamab across the COVID-censored analyses with or without the inclusion of Cohort A.
</td>
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<tr>
<td>Comment 2b</td>
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Additional PFS2 analyses show consistency with and support the OS benefit for talquetamab

The OS benefit of talquetamab over teclistamab is clinically plausible, as detailed by the clinical experts during the ACM, as patients' immune function is improved following treatment with talquetamab compared to following treatment with teclistamab (also see Appendix 3). This improved immune fitness is due to less compromised humoral immunity meaning patients are able to fight infections more vigorously and are not subject to the associated comorbidities that come with repeated infections (see further discussion on humoral immunity in Comment 2c).[4-6] The Q2W dosing regimen of talquetamab may also contribute to the improved immune fitness; patients receiving teclistamab may do so on a weekly regimen, and patients can experience T cell exhaustion from this frequent treatment.[11, 12] Meanwhile, by receiving talquetamab every other week, patients T cells are able to reinvigorate and recover.[3 21] Patients receiving talquetamab therefore experience
</td>
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</table>

less severe T cell exhaustion and so are more likely to receive and respond effectively to subsequent treatments.

To further validate this, additional PFS analyses have been conducted to compare the progression-free status of patients following receipt of a subsequent treatment i.e., PFS2, to provide an understanding of outcomes of patients post-treatment with talquetamab or teclistamab. In these analyses, PFS2 is defined as the time between the study treatment start date and date of event (defined as progressive disease as assessed by investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first).

Two-stage adjustment for subsequent treatments not available in the UK was performed analogous to the two-stage adjustment in the Company submission (details of which are presented in Section 2.10.4).

The HR for PFS2 with the all-in two-stage adjustment (including both subsequent teclistamab treatment and subsequent talquetamab, as per the revised base case) is presented in Table 5. The KM curves are presented in Appendix 6.

Table 5. 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]	[redacted]
Weighting		
ATT + subsequent treatment adjustment + inclusion of talquetamab post-teclistamab and teclistamab post-talquetamab	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; PFS2: progression-free survival after subsequent treatment.

These analyses demonstrate that talquetamab significantly improved PFS2 compared to teclistamab (ATT weighted and subsequent treatment adjusted HR: [redacted](95% CI:[redacted] p=[redacted]). Results clearly demonstrate that the time to disease progression following a subsequent line of therapy is longer with talquetamab compared to teclistamab, further supporting the statistically significant and clinically meaningful survival benefit for talquetamab compared to teclistamab.

Clinical expert opinion (DGD, page 10) further supported that patients receiving talquetamab initially (i.e., MonumenTAL-1) had improved immune fitness compared with teclistamab (i.e. MajesTEC-1), with fewer infections experienced and less severe T cell exhaustion. As such,

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	and shown by the PFS2 results, patients are able to derive additional benefits from subsequent treatments following treatment with talquetamab compared to following treatment with teclistamab.
Comment 2c	**All ITC analyses, before and after COVID-19 censoring, and additional PFS2 analyses support the significant OS benefit in favour of talquetamab. Reasons for this OS benefit are multi-faceted** [redacted] • ***Impact of treatment on humoral immune fitness (ability to produce antibodies)*** • ***Impact of T cell exhaustion on response to subsequent therapies*** To address the concerns raised by the Committee on the uncertainty of the OS ITC HR, the Company has provided a comprehensive set of additional analyses, namely (1) Censoring for COVID-19 deaths in the ITC analyses (Comment 2a), (2) Providing ITC results where Cohort A+C data (unweighted and 10:90 weighted) are used to inform the efficacy of talquetamab (Comment 1), and (3) PFS2 analyses to further validate the clinical rationale underpinning the OS benefit (Comment 2b). In addition to these analyses, the Company has provided below further rationale and evidence that supports the presence of a significant OS benefit in favour of talquetamab over teclistamab. ***Impact of treatment on immune fitness*** As described in the Company submission, it is clinically plausible that the OS benefit may be attributed to [redacted][10, 22-27] As widely supported by literature, by targeting GPRC5D (which is not expressed on cells implicated in humoral immune function), talquetamab allows for **reduced suppression of humoral immunity** compared to BCMA-targeting drugs, such as teclistamab, as BCMA is essential for the humoral immune response.[4-6] One study demonstrated the lower infection rates (particularly rates of fatal infections) with talquetamab compared to BCMA-targeting T-cell based therapies, in line with findings from an additional study comparing the proportion of Grade ≥3 infections experienced with GPRC5D and BCMA-targeting BsAbs (36% vs. 58%, respectively; p=0.04).[4, 28] Approximately 20% of patients experienced Grade 3/4 infections with talquetamab (mostly during cycles 1–2), with low rates of opportunistic infections, discontinuation, and death.[4] The data also demonstrated potential humoral immunity recovery with talquetamab

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(evidenced by increased non-clonal immunoglobulin [Ig]G levels not seen with BCMA-targeting BsAbs) is accompanied by rapid and durable responses.[4, 5]

These results are further supported by a recent analysis of parameters of humoral immunity in patients in MonumenTAL-1.[6] After a median follow-up of 12.7 months for patients in Cohort C, in patients receiving talquetamab:

- Neutrophil levels recovered at cycle 2 and were maintained throughout treatment
- B cell levels were stable in early cycles and increased at cycle 7
- IgG levels recovered after cycle 3 and increased up to cycle 17.

Patients treated with talquetamab were therefore considered to have preserved their humoral immunity.[6]

Meanwhile, a study investigating the impact of BCMA-targeting BsAbs on humoral immunity has shown that there is a significant decrease in polyclonal IgG, IgA, IgE and IgM levels after the start of treatment which showed no recovery over time.[5] In *ex vivo* assays, teclistamab treatment induced rapid depletion of peripheral blood B cells in patients with MM and eliminated normal plasma cells.[5] Consequently, responses to vaccines against various infectious diseases were severely impaired in patients who received teclistamab compared to patients with newly diagnosed RRMM.[5] Moreover, as talquetamab does not target patients' B cells, but rather the GPRC5D expressed on cancer cells, patients' B cell levels are preserved.[6] Subsequently, patients are at a lower risk of severe infections and hypogammaglobulinemia following talquetamab treatment compared to patients receiving teclistamab.[6, 7] [redacted][8-10]

Impact of T cell exhaustion on response to subsequent therapies

As noted by the Company during the ACM, following treatment with BCMA-targeting BsAbs patients' T cells may not respond effectively to further TCR therapies as they experience T cell exhaustion.[11, 12] T cell exhaustion with teclistamab treatment is linked with its dosing regimen, as mandated in the SmPC; it is administered every week. This continuous exposure induces persistent antigen stimulation leading to declining T cell function over time and possibly the loss of T cell function. Without fully functional T cells, the patient is unable to respond to subsequent therapies to fight myeloma, and therefore progresses. It is plausible, that longer treatment-free intervals reduce T cell exhaustion. One study has shown that patients receiving teclistamab with a lower frequency of T cells expressing exhaustion markers have improved PFS compared to those with higher levels of T cell exhaustion.[11] Treatment-free intervals beyond that observed with teclistamab treatment can be achieved with talquetamab via the Q2W dosing, as soon as the patient completes the

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step-up dose.[21] The Q2W dosing with talquetamab allows T cells to reinvigorate before the next dose of bispecific.[3] Over time, the T cell function is preserved from exhaustion and can continue to sustain survival gains with subsequent therapies.

The increased immune fitness of patients following talquetamab treatment as well as the preserved T cell function is supported by the additional PFS2 ITC analyses presented in Comment 2b, in which talquetamab showed significant improvements in PFS2 compared to teclistamab (HR for all in scenario: [redacted] [95% CI: [redacted]; p=[redacted]). These analyses therefore support that the OS benefit in favour of talquetamab can, in part, be attributed to the improved fitness and the less severe T cell exhaustion of patients following progression on talquetamab compared to progression on teclistamab.

Early separation in the OS KM curves for talquetamab and teclistamab

As detailed in the DGD (p10), the Committee noted that there is notable early separation in the OS KM curves for talquetamab and teclistamab (Figure 20 in the Company submission; Section 2.10.5), and there was no clear explanation for this. The Company notes that the early drop in OS curve for teclistamab is consistent across BCMA BsAbs.[14, 15]

To further characterise this separation, Table 6 summarises the number of deaths during the first three months of the MonumenTAL-1 and MajesTEC-1 trials. There were more than [redacted] as many deaths in MajesTEC-1 compared to MonumenTAL-1 during the first three months ([redacted]% compared to [redacted]%, respectively).[7, 13] In both treatment arms, the majority of deaths were caused by disease progression ([redacted]% in MajesTEC-1 compared to [redacted]% in MonumenTAL-1, respectively).[7, 13] It should be noted that despite the higher number of COVID-19 deaths in MajesTEC-1 compared to Cohort C of MonumenTAL-1, this early separation in OS KM curves cannot be solely attributed to COVID-19 as illustrated by the COVID-censored results in Comment 2a.

Time to best response is faster on treatment with talquetamab compared with teclistamab. Time to best response was [redacted] months (range: [redacted]) in MonumenTAL-1 and [redacted] months (range: [redacted]) in MajesTEC-1.[7, 13] Faster deep responses to treatment allow for myeloma plasma cell clearance, patient recovery and reduced mortality earlier in the course of treatment.

This early progression with teclistamab correlates to a lower ORR in MajesTEC-1 (63.0%) compared with talquetamab in MonumenTAL-1 (69.5%); further supported by significant ORR benefit of talquetamab over teclistamab in the ITC performed in the Company submission (Section 2.10.5; ORR ATT-adjusted relative risk [RR]: [redacted] [95% CI: [redacted]); p=[redacted]).[13, 29]

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Table 6. 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]

Abbreviations: AE: adverse event.
Source: J&J IM. Data on File. Deaths during the first three months of MonumenTAL-1 (September 2024 DCO) and MajesTEC-1 (August 2023 DCO).[30]

Summary

The Company has provided a comprehensive set of additional analyses and rationale to address the concerns highlighted by the Committee as part of the ACM and DGD, and to minimise the uncertainty associated with the ITC OS HR. The COVID-censored ITC analyses presented as part of this response (Comment 2a), clearly provide evidence of a significant survival benefit in favour of talquetamab once the impact of COVID-19 has been accounted for, while additional PFS2 analyses further support that patients have fitter humoral and cell-mediated immunity following disease progression on talquetamab than on teclistamab.

All analyses clearly support that there is a significant OS benefit in favour of talquetamab, [redacted][10, 22-27][redacted] With their immune fitness preserved, patients receiving talquetamab are able to effectively prolong survival gains with subsequent therapies compared to those initially treated with teclistamab.

Comment 3

SACT data for talquetamab and teclistamab

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<table>
<tr><td></td><td>The Company will provide a separate response considering the SACT data provided by NICE.</td></tr>
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The revised Company base case including the impact of COVID-19 censoring is consistent with economic results without censoring for COVID-19, demonstrating that COVID-19 censoring has a minimal impact on the cost-effectiveness of talquetamab

To account for the impact of censoring patients who died from COVID-19 in MonumenTAL-1 (Cohort C) or MajesTEC-1 (as outlined in Comment 2a) on the economic results, the Company has revised the base case economic analysis to include the COVID-censored HR derived from the base case COVID-censoring analysis described in Comment 2a. An alternative approach (censoring all patients with COVID-related death) was explored as a scenario analysis. Additional scenario analyses were also conducted using the 10%:90% weighted Cohort A + C data from MonumenTAL-1.

The results of the revised base case, as well as the alternative COVID-19 censoring scenario analysis, are summarised in Table 7. The proportional hazards (PH) assumption tests detailed in Appendix 5 show no violation of PH across the uncensored and COVID-19 censored scenarios, meaning that the HR approach is appropriate. All analyses include the impact of subsequent talquetamab and teclistamab following initial treatments as per the revised base case.

These results demonstrate that, at their respective PAS prices, inclusive of the revised PAS for talquetamab (reported above), the approach to COVID-censoring has a minimal impact on the ICER. All analyses result in ICERs below or close to the appropriate ICER threshold of £30,000/QALY. It can therefore be concluded that the Company economic analysis is robust to the approach of COVID-censoring.

Table 7. Summary of revised base case and scenario analysis results exploring the impact of COVID-19 (talquetamab and teclistamab PAS price[a,b]) – deterministic

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
	Revised base case (censor all COVID-related deaths that did not progress before and had CR+ as best response; Cohort C) (HR: [redacted])	[redacted]	[redacted]	***£28,005***	***0.10***
1	HR modelling approach using the non-COVID adjusted OS HR for Cohort C (HR: [redacted])	[redacted]	[redacted]	£25,727	0.25

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	2	HR modelling approach using the alternative COVID-adjusted OS HR approach for Cohort C (HR: [redacted])	[redacted]	[redacted]	£30,951	−0.04
	3	HR modelling approach using the non-COVID adjusted OS HR for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	26,138	0.21
	4	HR modelling approach using the base-case COVID-adjusted OS HR approach for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	28,401	0.08
	5	HR modelling approach using the alternative COVID-adjusted OS HR approach for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	31,446	−0.06
	Footnote: [a] Inclusive of revised PAS discount for talquetamab of [redacted]%. [b] Post-subsequent treatment adjustment including subsequent talquetamab and teclistamab. **Abbreviations:** CR+: complete response or better; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.					
Comment 5	**Independent modelling scenarios have been provided and have limited impact on the ICER. However, the HR approach is the most appropriate approach to assess the cost-effectiveness of talquetamab and teclistamab. The HR approach accurately reflects the treatment effect observed in the robust ITCs and is grounded on an objective assessment of the best available data rather than subjective assumptions required for the independent modelling approach** As requested by the Committee in the DGD, the Company has provided further analyses in which the long-term estimates for OS, PFS and TTD are derived independently and without calibration to clinical expert estimates. These analyses are presented below. These have been provided as scenarios only as the Company strongly considers that the HR approach adopted in the initial submission (Section 3.3), in which the long-term extrapolations of OS, PFS and TTD for talquetamab were derived by applying HRs from the base case ITCs to the teclistamab reference curves in TA1015, to be the most appropriate approach for the following reasons:					

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	1. **PH assumption clearly holds:** As discussed in the Company submission (Section 3.3), there is no evidence that that the PH assumption is violated (see Figure 19 and Figure 20 in Appendix 5); thus, the HR approach is the most appropriate methodology for generating long-term survival estimates for talquetamab, in line with NICE technical support document (TSD)14.[16] 2. **EAG is in agreement with the Company that the PH-based approach is justified:** Importantly, the EAG noted in their critique (Section 3.4.6.1) that they agree a PH-based approach is justified for the comparison of talquetamab and teclistamab, because the PH assumption is not violated. The EAG's preferred assumptions (Section 5.3 of the report) utilises the same HR approach adopted in the Company submission, using a different extrapolation for the teclistamab curves. The EAG expressed concern that the HR from the ITC was applied to an accelerated failure time (AFT) model in the Company base case (LogNormal). However, this concern has been mitigated in the Company's revised base case analyses as part of this response, in which the Weibull extrapolation has been adopted for the long-term survival outcomes for teclistamab, in line with the EAG base case. 3. **The HR approach is associated with significantly less uncertainty than the independent modelling approach and is grounded on the best available evidence**: This approach incorporates the ITC results directly, ensuring the accuracy of the treatment effect and the clinical plausibility of the economic model. Moreover, the robustness of the ITC cannot be underestimated wherein the Company had access to the IPD of both trials and were therefore able to ensure relevant patient baseline characteristics were well-matched and provide long-term extrapolations which are grounded in observed data. The independent modelling approach relies on subjective assumptions and therefore, is linked with more uncertainty. Concerns raised by the Committee regarding the uncertainty associated with the HR approach have been addressed by the Company through the provision of additional analyses requested which show consistent results and an OS benefit associated with talquetamab over teclistamab. In response to the Committee's request, additional scenarios have been explored by the Company as part of this response, which are discussed further below. Additional information on the independent modelling scenarios is provided in Appendix 7, with the results presented in Table 8 and a full list of scenario analyses presented in Appendix 2. • Scenario 6: Weibull for teclistamab OS, PFS and TTD, Gamma for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)

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	• Scenario 7: Weibull for teclistamab OS, PFS and TTD, Weibull for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all) The Company has also provided additional modelling results using the 10:90 pooled, weighted Cohort A and C data in the following scenarios: • Scenario 8: Weibull for teclistamab OS, PFS and TTD, Gamma for talquetamab (10:90 weighted Cohort A+C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all) • Scenario 9: Weibull for teclistamab OS, PFS and TTD, Weibull for talquetamab OS (10:90 weighted Cohort A+C), LogNormal for talquetamab PFS and TTD (uncalibrated for all) ***Teclistamab extrapolations – OS, PFS and TTD*** In all scenarios explored, the uncalibrated Weibull distribution is used to extrapolate the OS, PFS and TTD for teclistamab. The Weibull distribution is aligned with the EAG's base case analyses in the EAG report (Section 5) and the Committee's view in the DGD as it does not require calibration in order to reflect clinician estimates. ***Talquetamab extrapolations*** *PFS and TTD extrapolations* In all scenarios, the uncalibrated LogNormal distribution is used to extrapolate PFS and TTD for talquetamab. As noted in Table 65 and Table 66 of Appendix K.2 and Appendix K.3 in the Company submission, respectively, the LogNormal distribution provides the best statistical fit for both outcomes in terms of Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. The long-term extrapolations for talquetamab (Cohort C) PFS and TTD are presented in Figure 1 and Figure 2 below, respectively. The long-term PFS and TTD extrapolations for talquetamab (pooled, 10:90 weighted Cohort A+C) are presented in Appendix 7 (Figure 35 and Figure 36, respectively).

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Figure 1. Long-term PFS extrapolations for talquetamab (Cohort C)

Abbreviations: PFS: progression-free survival.

Figure 2. Long-term TTD extrapolations for talquetamab (Cohort C)

Abbreviations: TTD: time to treatment discontinuation.

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	OS extrapolations Based on the AIC and BIC values, as presented in Table 17 (Appendix 7), the Gompertz and LogNormal distributions are the two best statistically fitting distributions for OS. However, both of these distributions appear to predict high proportions of patients still alive after 20 years (Figure 3; ~[redacted]% for LogNormal and ~[redacted]% for Gompertz) and were hence ruled out as being less clinically plausible; as were the LogLogistic and Generalised Gamma distributions. The exponential distribution was strongly considered to be inappropriate and therefore excluded: • As agreed by the EAG (Section 3.4.6.1 of the EAG report) the exponential distribution provides the worst statistical fit to the observed talquetamab OS data and an extremely poor visual fit (as shown in Figure 3). • The exponential distribution also assumes a constant hazard of death – which is completely contradictory with the observed data from the MonumenTAL-1 trial (Figure 4). The constant hazard of death over time assumed by the exponential distribution is not clinically plausible, especially considering the disease biology of RRMM and how the risk of death can vary over time depending on initial response to treatment.[17] All of the available evidence suggests that a constant hazard of death is not clinically plausible and does not reflect the disease biology or the trial data, and therefore the exponential was excluded from further consideration. • The exponential distribution lacks clinical plausibility given that it results in a completely unrealistic implied HR over time with an average HR of [redacted] in the first 20 years which increases beyond a HR of [redacted] at certain points (see Figure 5). This implies that patients would be at a higher risk of death on talquetamab versus teclistamab – directly contradicting the trial data. Further, the implied HR exceeds [redacted] before 2 years, which does not reflect the available trial data and ITC results. This provides further justification to reject the exponential distribution to model OS whereas the Weibull and Gamma distributions can provide alternative plausible landing points.

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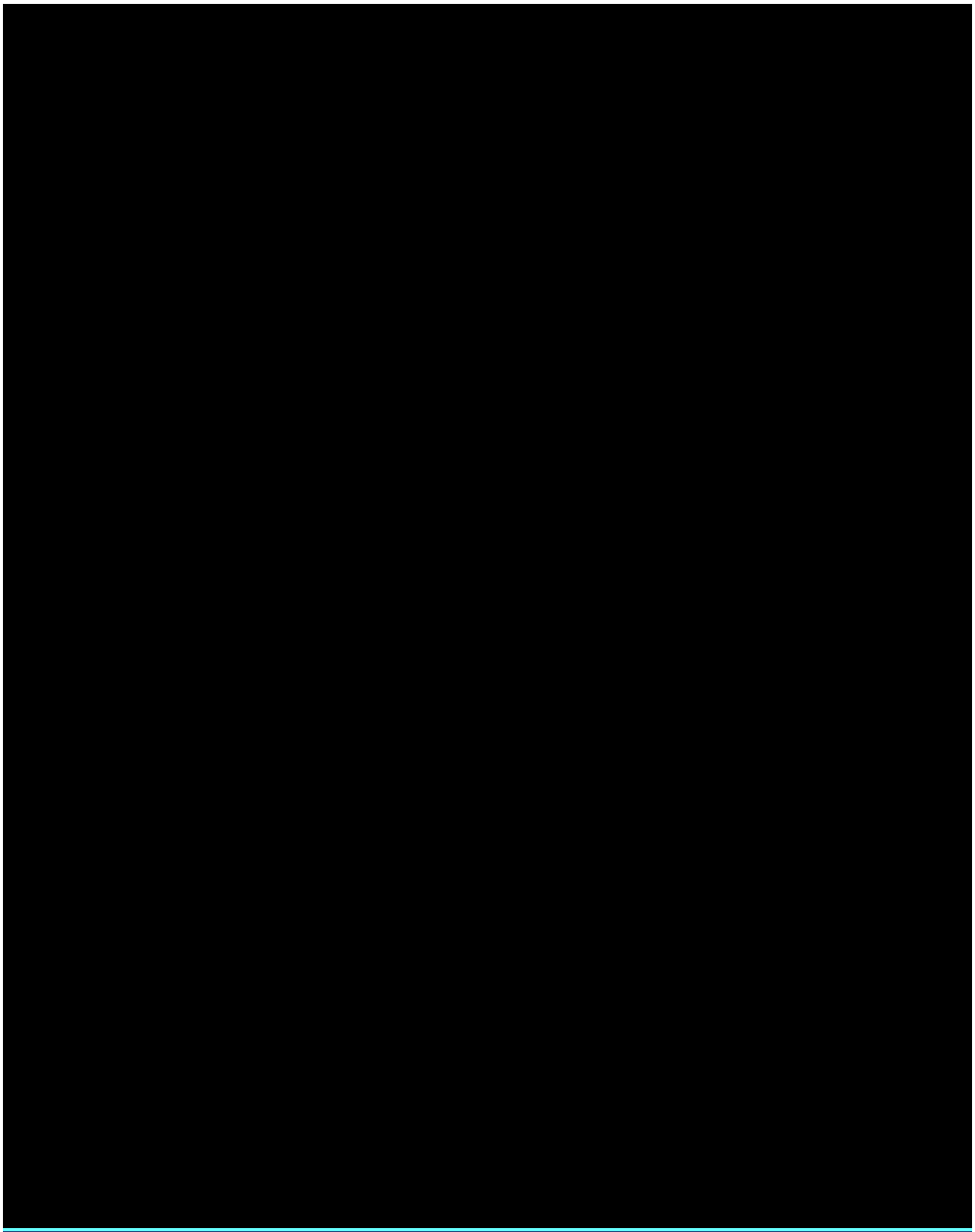
Figure 3. OS extrapolations for talquetamab (Cohort C), ATT (n=17) (base case subsequent treatment adjustment) (A) zoomed-in from Year 0 to 5, and (B) for the whole time horizon



Abbreviations: ATT: average treatment effect for the treated; DCO: data cut-off; OS: overall survival.
Source: J&J IM. Data on file. Analysis based on MonumenTAL-1 Clinical Study Report (September 2024 DCO).[31]

Figure 4. Hazard plot for talquetamab (Cohort C) OS, ATT (n=17)

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	 **Abbreviations**: ATT: average treatment effect for the treated; DCO: data cut-off; OS: overall survival. **Source:** J&J IM. Data on file. Analysis based on MonumenTAL-1 Clinical Study Report (September 2024 DCO).[31]

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Figure 5. Implied HR for the exponential extrapolations of talquetamab (Cohort C) OS

Abbreviations: HR: hazard ratio; OS: overall survival; Tal: talquetamab; Tec: teclistamab.

Based on the reasons stated above, the Company considers the Gamma or Weibull distributions to be suitable to extrapolate long-term outcomes with talquetamab as they represent the two clinically plausible curves with the lowest predictions of OS extrapolations for talquetamab. The results of the scenario analysis are presented below in Table 8. However, as outlined in Comment 4, the Company considers that the HR approach is more appropriate than individually fit curves for the comparison of talquetamab and teclistamab, and thus have retained this in the model base case.

Independent modelling scenario results

The results of the independent modelling scenarios are summarised in Table 8. These results demonstrate that the modelling of efficacy outcomes using independently applied survival extrapolations leads to small increases in incremental costs, over the HR approach, for all scenarios explored. Similar trends were observed for the incremental QALYs generated using the independently fitted survival extrapolations, with only Scenario 8 generating lower incremental QALYs to the base case HR approach.

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In line with that observed for the COVID-censoring scenarios discussed in the response to Comment 2a, the cost-effectiveness results for the independent modelling scenarios are broadly in line with the revised base case analysis and aggregate below, or in close proximity to, the appropriate WTP of £30,000/QALY. Thus, the Company revised economic analysis is robust to the extrapolation approach (HR modelling or independent modelling), minimising the uncertainty associated with the method adopted by the Company in the base case analyses.

Table 8. Summary of revised base case and scenario analysis results exploring independent modelling of the talquetamab and teclistamab survival extrapolations (talquetamab and teclistamab PAS price[a,b]) – deterministic

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
	Revised base case (using HR approach; censor all COVID-related deaths that did not progress before and had CR+ as best response; Cohort C) (HR: [redacted])	[redacted]	[redacted]	***£28,005***	***0.10***
6	Weibull for teclistamab OS, PFS and TTD, **Gamma** for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£31,652	−0.09
7	Weibull for teclistamab OS, PFS and TTD, **Weibull** for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£27,942	0.13
8	Weibull for teclistamab OS, PFS and TTD, **Gamma** for	[redacted]	[redacted]	£33,208	−0.16

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		talquetamab (10:90 weighted Cohort A+C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)				
	9	Weibull for teclistamab OS, PFS and TTD, **Weibull** for talquetamab (10:90 weighted Cohort A+C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£29,237	0.04

Footnote: [a] Inclusive of revised PAS discount for talquetamab of [redacted]%. [b] Post-subsequent treatment adjustment including subsequent talquetamab and teclistamab.
Abbreviations: ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

Comment 6

Using alternate parametric distributions for the two-stage subsequent treatment adjustment has a negligible impact on the ITC results, thereby minimising any uncertainty with this adjustment

As noted in Section 2.7 of the CS, due to the international nature of the MonumenTAL-1 and MajesTEC-1 clinical trials, the subsequent treatments received by patients in both MonumenTAL-1 and MajesTEC-1 do not fully reflect UK clinical practice.

As such, the data for MonumenTAL-1 and MajesTEC-1 were adjusted using a two-stage OS adjustment approach, in line with NICE TSD 16, to remove the effects of subsequent treatments which are not routinely available in UK clinical practice.[16] The methods for this adjustment are discussed in Section 2.10.4 of the Company submission, supplemented by the Company clarification responses to questions A12–A14. As noted on p.82 of the EAG report, the EAG considered the Company's two-stage adjustment approach to remove the effects of subsequent treatment(s) not routinely available in the UK on OS, to be methodologically appropriate.[20]

As requested by the Committee in the DGD, the Company has provided a more detailed explanation of the overall methods used to adjust for subsequent treatments not available in NHS clinical practice. Table 9 presents the acceleration factors and AIC statistics when the different parametric distributions were explored. The acceleration factor was consistent

across all parametric distributions explored for talquetamab, with comparable model fit as indicated by the AIC. However, a wider range of acceleration factors was observed for teclistamab. The AIC value indicated that the Gamma distribution should be selected as the best model for teclistamab, but given that its acceleration factor was considerably higher ([redacted]) compared to the other distributions (ranging from [redacted] [LogNormal] to [redacted] [Weibull]), a conservative approach was taken (in terms of the ITC of talquetamab versus teclistamab) by choosing the next best fitted model, i.e. the Weibull distribution.

For these reasons, in the original Company base case, the Weibull distribution was chosen as the extrapolation to inform the two-stage subsequent treatment adjustment. It should however be noted that use of alternate parametric distributions in the two-stage adjustment led to consistent OS HRs for treatment with talquetamab compared to teclistamab, thereby demonstrating the Company base case ITC analysis to be robust to uncertainty regarding the selected distribution to inform subsequent treatment adjustment.

Table 9. Acceleration factors and AIC values for alternative parametric distributions for the two-stage adjustment

Distribution	AF	AIC	AIC unlogged response
Talquetamab			
Exponential	[redacted]	[redacted]	[redacted]
Weibull (original Company base case)	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]
Teclistamab			
Exponential	[redacted]	[redacted]	[redacted]
Weibull (original Company base case)	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]

Abbreviations: AF: acceleration factor; AIC: Akaike information criterion.

Results of alternative parametric distributions in the two-stage adjustment

As requested by the Committee in the DGD, the Company has provided additional analyses using alternative parametric distributions in the AFT model. HRs and the respective p-values

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for the OS analyses using alternative parametric distributions in the two-stage adjustment are presented in Table 10 below. The full range of KM curves for the conducted analyses are presented in Appendix 8.

Table 10. Comparison of OS between talquetamab (Cohort C) and teclistamab (before and after ATT weighting; including subsequent talquetamab and teclistamab)

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

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

When using the alternative distributions, the OS HRs for treatment with talquetamab compared to teclistamab ranged from [redacted] (95% CI: [redacted]) for the two-stage adjustment using the Gamma distribution to [redacted] (95% CI: [redacted]) using the LogNormal distribution. These results were highly consistent with the Company's approach of using the Weibull distribution in the AFT model thereby minimising any uncertainty with this adjustment.

Comment 7

The Company have included the disutility associated with dysgeusia in the revised base case, which had a minimal impact on the ICER

As noted in Section 3.4.4 of the CS, the base case economic analyses included one-off decrements in utility for Grade ≥3 AEs occurring in at least 5% of patients in MonumenTAL-1 or MajesTEC-1. Through this approach, the impact of dysgeusia was not included because it cannot be classed as higher than Grade 2 in clinical practice.[29]

The Company acknowledges the Committee's view in the DGD that altered taste (and subsequent weight loss) may impact quality of life (DGD, p18). As requested by the Committee, the Company has provided more explicit modelling of AE disutilities and impact of altered taste (and weight loss) and have updated the base case (see Appendix 1) as follows:

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	• In the absence of Grade ≥3 dysgeusia, patients experiencing Grade 2 dysgeusia were included in the model. This was considered appropriate based on differences in the severity of symptoms between Grade 2 versus Grade 1 dysgeusia. As per the CTCAE grading scale, Grade 2 dysgeusia is associated with altered taste with change in diet and therefore more likely to lead to weight loss / impact quality of life compared to Grade 1, where symptoms are mild (i.e., altered taste but diet unchanged).[32] • The duration of the AE in days (mean duration in Cohort C: [redacted] days [SD: [redacted]) as well as the proportion of patients experiencing it (Grade 2 dysgeusia proportion: [redacted]%) were sourced from the MonumenTAL-1 trial.[7] • Dysgeusia disutility (-0.02) was applied in line with the other AE disutility decrements in the model (see Section 3.4.4 of the Company submission), and informed by published literature (Gumbie, *et al.* 2021).[33] As discussed during the ACM and in Section 2.11.4 of the Company submission, dysgeusia can be adequately managed in clinical practice and only led to a small proportion of patients having their talquetamab dose modified ([redacted]%) , reduced ([redacted]%) or discontinued ([redacted]%) in MonumenTAL-1 (Cohort C; September 2024 DCO).[7] Furthermore, as shown in Appendix 1, the inclusion of the AE disutility decrement for dysgeusia has a minimal impact on the ICER. In relation to the Committee's request for more explicit modelling of associated weight loss, the Company would like to clarify that the original economic model included an AE disutility for patients experiencing Grade ≥3 weight loss (see Section 3.4.4 of the Company submission), so this AE is already suitably accounted for within the economic model.
Comment 8	**In light of the high unmet need in the TCE RRMM setting, uncaptured benefits in the economic analysis and the additional analyses that consistently demonstrate the magnitude of OS benefit for talquetamab versus teclistamab, an ICER threshold of £20,000 per QALY gained is inappropriate** The Company is extremely disappointed with the Committee's conclusion that *"an acceptable ICER [for talquetamab compared to teclistamab] would be around £20,000 per QALY gained*" due to the uncertainties in the evidence base and analysis from the first Committee meeting. The Company considers that a willingness-to-pay threshold close to the upper end of the range normally considered cost-effective would be appropriate for this appraisal. This is in light of:

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	• The extensive scenario analysis provided in this response and body of evidence considered which provide reassurance and certainty regarding the clinical and cost-effectiveness of talquetamab • The potential benefits provided by talquetamab, demonstrated in terms of patient outcomes and reinforced by the views expressed by clinical experts and patients • Application of these topics according to the NICE manual which notes that the degree of certainty around the ICER and aspects that relate to uncaptured benefits and non-health factors will influence the decision to select an ICER above £20,000/QALY Of particular relevance, the Company considers the following points as critical context for determining the ICER threshold: ***Critical unmet need in the TCE RRMM disease setting*** Whilst the Committee has clearly acknowledged the unmet need for more efficacious treatments in MM (DGD, p5), the Company does not consider that the significant unmet need in the TCE RRMM disease setting has been appropriately reflected by the Committee in determining the ICER threshold for talquetamab. Despite the step-change in the treatment pathway with the advent of teclistamab, TCE RRMM remains a terminal, end of life illness, with a median OS of less than 24 months.[17] Alternative treatment options such as talquetamab are therefore desperately needed to enhance patients life expectancy and provide patient and clinicians choice; a fundamental aspect of NHS care.[18, 19] UK clinical experts reaffirmed that an unmet need exists for TCE RRMM treatments with alternative targets that are associated with a lower risk of severe infections than BCMA-targeting treatments like teclistamab.[1] Such treatments could in turn reduce the impact of infections on both patients' QoL and the NHS resources via reduced need for IVIg administration (as discussed in the Company submission, Section 2.11.4).[1] Moreover, the RRMM treatment landscape is evolving, with ongoing changes in therapeutic approaches, including the introduction of more BCMA-targeted treatments earlier in the treatment pathway in the UK (such as belantamab mafodotin with bortezomib and dexamethasone in the second-line setting [ID6212]).[34], There may be an increasing unmet need over time for treatments such as talquetamab, that have a distinct target to BCMA, at later lines of therapy. Patients who had prior exposure to belantamab mafodotin were not excluded from the MonumenTAL-1trial. By targeting GPRC5D, talquetamab presents a compelling alternative option to BCMA-targeting treatments for TCE RRMM patients, that provides incremental survival gains and

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an improved infection-related safety profile compared to teclistamab; thereby addressing the existing unmet needs in this setting.

The outstanding uncertainty associated with the comparison of talquetamab versus teclistamab identified by the Committee has been fully addressed in this response and the revised Company base case

The Committee noted in the ACM and in the DGD that there were uncertainties in the OS results for the ITC comparing talquetamab and teclistamab. The Company disagree that the clinical evidence base is highly uncertain given the strengths of the ITC conducted. As discussed in Section 2.10.7 of the Company submission, the Company performed a highly robust ITC, using individual patient data (IPD) for both the MonumenTAL-1 and MajesTEC-1 clinical trials. Because of this, the MajesTEC-1 baseline characteristics were able to be adjusted across all 17 key covariates identified by clinical experts, resulting in standardised minimum difference (SMD) scores <0.2 for all variables. HTA experts consulted by the Company also acknowledged that the ITC approach was highly robust and in line with the best practices outlined by NICE.[35]

As part of this response, the Company has provided additional analyses requested by the Committee to address areas of uncertainty highlighted in the DGD. All analyses clearly demonstrate that there is a substantial OS benefit in favour of talquetamab, [redacted].[3]

Firstly, the clinical effectiveness comparison results using data pooled from Cohorts A+C of the MonumenTAL-1 trial demonstrate consistency with the results using Cohort C only, and continue to show a statistically significant survival benefit in favour of talquetamab (see Comment 1).

Secondly, the COVID-censored ITC analyses presented as part of this response also demonstrate that the significant OS benefit in favour of talquetamab is still observed when patients who died due to COVID-19 in MonumenTAL-1 and MajesTEC-1 are censored (Comment 2a). The results of the two scenarios presented in Comment 2a (OS HR: [redacted] and [redacted]) are consistent with the base case ITC results from the Company submission (including the impact of both subsequent talquetamab and teclistamab; OS HR: [redacted]

To further characterise the OS benefit, the Company has additionally provided the results of PFS2 analyses for the ITC of talquetamab and teclistamab in Comment 2b. These results demonstrate that talquetamab was associated with a significant improvement in PFS2 compared to teclistamab (HR: [redacted] [95% CI: [redacted]]; p=[redacted]) and clearly support that patients are able to derive additional benefits from subsequent treatments following treatment with talquetamab compared to following treatment with teclistamab.

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	Finally, the Company has provided a revised base case analysis (see Appendix 1): that included all of the Committee's preferred assumptions listed in the DGD (page 19) as outlined below • Including the costs and benefits of subsequent talquetamab and teclistamab following initial treatment (note: In the original Company based case, subsequent teclistamab use was included) • Using the MonumenTAL-1 and MajesTEC-1 trials to inform the proportions of patients receiving IVIg with talquetamab and teclistamab, respectively (note: this approach was taken in the original Company base case wherein IVIg use were modelled for initial talquetamab and teclistamab as well as subsequent talquetamab. Subsequent talquetamab was not modelled in the original Company base case but this has since been revised). • Including the proportions of subsequent IVIg for talquetamab and teclistamab, informed by MonumenTAL-1 and MajesTEC-1 respectively • Discounting costs and QALYs from the second year of the model • Excluding the costs and QALYs associated with half-cycle correction • As outlined by the Committee on page 20 of the DGD, and in recognition of the potential impact on quality of life, the Company has also now included the impact of altered taste and associated weight loss, by including an AE disutility for Grade 2 dysgeusia ***Benefits not captured in the economic analyses*** The Company strongly considers there are key benefits of talquetamab that have not been captured in the economic analyses (as discussed in Section 3.13 of the Company submission) which the Committee has not taken into account. The value of hope, reductions in anxiety associated with the introduction of talquetamab and the benefits of its novel target are not accounted for in the modelling approach. The introduction of talquetamab would allow clinicians to tailor treatment to patients' individual needs mitigating the current lack of clinician and patient choice. The lower rate of infections associated with talquetamab compared to teclistamab also means that patients are likely to experience reduced infection-related anxiety due to social isolation compared to those receiving BCMA-targeting BsAbs; an aspect which is not captured by the economic analyses. Additionally, a recent study sponsored by J&J IM surveying 120 carers of patients with MM found that in total, [redacted]% of the carers were partners or spouses of the patient.[36] With the flexible dosing regimen (discussed in Section 1.2 of the Company submission) and

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	improved infection-related safety profile associated with talquetamab, patients will be required to visit hospital less frequently, which consequently means the impact on their caregivers will also reduce. ***Conclusion*** The Company has provided a comprehensive set of additional analyses as part of this response as requested by the Committee and revised their base case economic analyses to include all of the Committee's preferred assumptions and minimise any uncertainty in the clinical evidence base and the economic model for talquetamab. Given the reduced uncertainty, high unmet need in the TCE RRMM setting and uncaptured benefits in the economic analysis, a willingness-to-pay threshold of £20,000 per QALY gained is inappropriate and should be reconsidered. With successive lines of therapy myeloma plasma cells acquire new genetic alterations and mutate to become resistant to treatment. Therefore, there remains a significant unmet medical need in TCE RRMM for effective treatments with alternative targets, such as GPRC5D. The substantially reduced uncertainty reflected in the revised base case, updated PAS discount, and supplementary analyses appropriately supports the Committee in determining the most likely cost-effectiveness estimate and making a positive recommendation for talquetamab.

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Appendices

Appendix 1. Committee-preferred assumptions applied in the cost-effectiveness analysis and updated Company base case

The cumulative changes to the Company cost-effectiveness estimates, including the Committee-preferred assumptions are presented in Table 11, with the revised base case results presented in Table 12 (probabilistic results) and Table 13 (deterministic results).

Following inclusion of all Committee-preferred assumptions, talquetamab represents a cost-effective use of the NHS resources compared with teclistamab when considering an appropriate willingness-to-pay (WTP) threshold of £30,000/QALY (see Comment 8).

Table 11. Cumulative changes to the company's cost-effectiveness estimates (deterministic results; PAS price[a])

	Talquetamab vs. teclistamab ICER (Costs per QALY gained)
Company's base case (at clarification questions)[b]	£29,277
Model updates: Committee-preferred assumptions applied[b] • Including the costs and benefits of subsequent talquetamab and teclistamab following initial treatment[c] • Aligning the extrapolations of teclistamab with the EAG- and committee-preferred approach of selecting the uncalibrated Weibull across OS, PFS & TTD • Including the proportions of subsequent intravenous immunoglobulin (IVIg) for talquetamab and teclistamab, informed by MonumenTAL-1 and MajesTEC-1 respectively • Discounting costs and QALYs from the second year of the model • Excluding the costs and QALYS associated with half-cycle correction	£29,940
Comment 7: Inclusion of disutility associated with Grade 2 dysgeusia (-0.02)[b]	£29,985
Comment 2a: Update OS HR ([redacted]) to COVID-19 censored OS HR ([redacted])[b]	£32,700
Updated base case following DGD response[a]	**£28,005**

Footnotes: [a] Inclusive of revised PAS discount for talquetamab of [redacted]%. [b] Inclusive of previous PAS discount for talquetamab of [redacted]%.[c] In the original Company based case, only subsequent teclistamab use was included.

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Abbreviations: DGD: draft guidance document; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; NHB: net health benefit; OS: overall survival; PAS: patient access scheme; QALY: quality adjusted life year.

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Table 12. Probabilistic DGD response base-case results (with PAS[a])

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Talquetamab	[redacted]	5.26	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	2.69	[redacted]	[redacted]	2.57	[redacted]	£28,534	0.08

Footnote: [a] Inclusive of revised PAS discount for talquetamab of [redacted]%.
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 13. Deterministic DGD response base-case results (with PAS[a])

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
Talquetamab	[redacted]	5.24	[redacted]	-	-	-	-	-
Teclistamab	[redacted]	2.66	[redacted]	[redacted]	2.58	[redacted]	£28,005	0.10

Footnote: [a] Inclusive of revised PAS discount for talquetamab of [redacted]%.
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Appendix 2. Summary of scenario analyses in the DGD response

A summary of the results of the scenario analyses conducted as part of this DGD response is presented in Table 14.

As discussed in the responses to Comment 4 and Comment 5, the results from the scenario analyses demonstrate close alignment with those of the revised base case. Only minimal differences were observed in incremental costs and QALYs – compared to the revised base case – upon varying the COVID-censoring approach (Scenarios 1 – 5) or through the use of independent survival extrapolations for talquetamab and teclistamab (Scenarios 6 – 9). These conclusions continue to hold true in scenario analyses informed using the 10:90 weighted Cohort A+C of MonumenTAL-1 (Scenarios 3 – 5, 8, 9).

Overall, these scenarios analyses demonstrate that the ICER is robust to potential areas of uncertainty raised in the DGD and therefore provide confidence that talquetamab represents a cost-effective use of NHS resources when assessed at the appropriate WTP threshold of £30,000/QALY.

Table 14. Summary of revised base case and scenario analysis results – deterministic (with PAS[a,b])

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000
Revised base case (using HR approach; censor all COVID-related deaths that did not progress before and had CR+ as best response; Cohort C) (HR: [redacted])		[redacted]	[redacted]	***£28,005***	***0.10***
1	HR modelling approach using the non-COVID adjusted OS HR for Cohort C (HR: [redacted])	[redacted]	[redacted]	£25,727	0.25
2	HR modelling approach using the alternative COVID-adjusted OS HR approach for Cohort C (HR: [redacted])	[redacted]	[redacted]	£30,951	−0.04
3	HR modelling approach using the non-COVID adjusted OS HR for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	£26,138	0.21
4	HR modelling approach using the base-case COVID-adjusted OS HR approach for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	£28,401	0.08

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5	HR modelling approach using the alternative COVID-adjusted OS HR approach for Cohort A+C (weighted 10:90; HR: [redacted])	[redacted]	[redacted]	£31,446	−0.06
6	Weibull for teclistamab OS, PFS and TTD, **Gamma** for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£31,652	−0.09
7	Weibull for teclistamab OS, PFS and TTD, **Weibull** for talquetamab (Cohort C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£27,942	0.13
8	Weibull for teclistamab OS, PFS and TTD, **Gamma** for talquetamab (10:90 weighted Cohort A+C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£33,208	−0.16
9	Weibull for teclistamab OS, PFS and TTD, **Weibull** for talquetamab (10:90 weighted Cohort A+C) OS, LogNormal for talquetamab PFS and TTD (uncalibrated for all)	[redacted]	[redacted]	£29,237	0.04

Footnotes: [a] Inclusive of PAS discount of [redacted]%. [b] Post-subsequent treatment adjustment including subsequent talquetamab and teclistamab.
Abbreviations: ICER: incremental cost-effectiveness ratio; HR: hazard ratio; INHB: incremental net health benefit; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year.

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Appendix 3. Factual inaccuracies

Page number	Quote from the DGD	Factual inaccuracy identified and rationale for requested correction	Correction requested
9	*"Regression-analysis studies on overall survival and progression-free survival (Etekal et al. 2023 and Cartier et al. 2015) indicate that the company's overall-survival hazard ratio is an outlier and is more favourable to talquetamab than would be expected given the progression-free survival hazard ratio (see section 3.6)."*	In the EAR, the EAG plotted the Company's HR results for teclistamab vs PomdDex and talquetamab vs teclistamab on two referenced regression analyses. However, it should be clarified that the studies used in regression analyses publications predate the use of bispecific treatments, such as talquetamab and teclistamab. The experts therefore stated that the Etekal, *et al* regression analysis may not be applicable as noted on Page 11 of the DGD. This is not currently clear from the bullet point on Page 9.	*"Regression-analysis studies on overall survival and progression-free survival (Etekal et al. 2023 and Cartier et al. 2015) indicate that the company's overall-survival hazard ratio is an outlier and is more favourable to talquetamab than would be expected given the progression-free survival hazard ratio (see section 3.6).* ***The studies used in these publications predate bispecific treatments with novel mechanisms of action and therefore clinical experts stated that the analyses may not be applicable****."*

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10	*"The company also said that people in MonumenTAL-1 were fitter than in MajesTEC-1. So, people were more likely to have subsequent treatments after talquetamab than after teclistamab."*	The Company did not state during the ACM that patients in MonumenTAL-1 were fitter than those in MajesTEC-1. Instead, as additionally discussed in Comment 2c of this response, the Company stated that, patients are likely to be of lower fitness following treatment with BCMA-targeting BsAbs compared to patients following treatment with GPRC5D-targeting BsAbs, as supported by published literature.[11, 12] This is because following BCMA-targeting treatments, patients' T cells may not respond as effectively to further TCR therapies as they experience T cell exhaustion.[11, 12] This means subsequent treatments may not be as effective following teclistamab, compared to talquetamab.	*"The company also said that* ***patients will be fitter following treatment with talquetamab compared to following treatment with teclistamab, as BCMA-targeting treatments can cause T cell exhaustion*** ~~*people in MonumenTAL-1 were fitter than in MajesTEC-1.*~~ *So, people were more likely to* ***respond more effectively to*** ~~*have*~~ *subsequent treatments after talquetamab than after teclistamab."*
14	*"But the committee was aware that the calibrated LogNormal model for progression-free survival and time to treatment discontinuation did not fit the observed Kaplan–Meier curves well despite having mature Kaplan–Meier data."*	The current statement in the DG that "*the calibrated LogNormal model for PFS and TTD did not fit the observed KM curves well"* is factually incorrect. As shown in Table 71 and Table 72 in Appendix K.2 and Appendix K.3 of the Company submission, respectively, the LogNormal distribution is the best statistically fitting curve in terms of AIC/BIC values. The LogNormal distribution additionally has a good visual fit to the KM data, as shown in Figure 3. As such, this statement should be corrected in the DGD.	*"*~~*But*~~ *the committee was aware that the calibrated LogNormal model for progression-free survival and time to treatment discontinuation* ***was the best statistically fitting curve*** ~~*did not fit the observed Kaplan–Meier curves well despite having mature Kaplan–Meier data*~~*."*

Abbreviations: ACM: appraisal Committee meeting; AIC: Akaike information criterion; BCMA: B cell maturation antigen; BIC: Bayesian information criterion; BsAbs: bispecific antibodies; DGD: draft guidance document; TCR: T cell redirecting.

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Appendix 4. Additional details on the ITC analyses for the pooled unweighted and 10:90 weighted MonumenTAL-1 Cohort A+C (Comment 1)

A summary of the results from the ITC analyses of talquetamab versus teclistamab, based on the trial data for patients in the pooled unweighted Cohort A+C of MonumenTAL-1 and patients in the MajesTEC-1 trial are presented in Comment 1. Details on the assessment of overlap and further details on the ITC results are presented in this appendix henceforth.

Assessment of overlap

Pooled, 10:90 weighted Cohort A+C

SMDs calculated before and after ATT weighting are presented in Table 15 and Figure 6, while histograms of PSs before and after weighting are depicted in Figure 7 and Figure 8. Similar to the ITC conducted between MonumenTAL-1 (Cohort C) and MajesTEC-1 in the Company Submission (Section 2.10.3), 15 of 17 prognostic variables adjusted for had an SMD ≤ ±0.2 prior to adjustment, suggesting there is a high level of alignment in the baseline characteristics of patients between the two cohorts (MonumenTAL-1 [pooled, 10:90 weighted A+C] and MajesTEC-1).

Following the adjustment for the 17 variables, none of the variables had an SMD above the threshold of 0.2, indicating that the adjustment process successfully balanced characteristics between studies (see Table 15). These alignments between the populations are also evident in the SMD plot in Figure 9 and histograms of the PSs, as shown in Figure 8.

Table 15. SMD for unadjusted and adjusted differences between MonumenTAL-1 (pooled, 10:90 weighted Cohort A+C) and MajesTEC-1 cohort

	Before adjustment			After adjustment		
	Talquetamab	Teclistamab	SMD	Talquetamab	Teclistamab	SMD
N	297	165	-	297	165	-
Refractory status, n (%)						
≤ double refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triple refractory	[redacted]	[redacted]		[redacted]	[redacted]	
Quad refractory	[redacted]	[redacted]		[redacted]	[redacted]	
≥ Penta refractory	[redacted]	[redacted]		[redacted]	[redacted]	
ISS						
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]		[redacted]	[redacted]	

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III	[redacted]	20 (12.1%)		[redacted]	[redacted]	
Time to progression on prior therapy						
<3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]		[redacted]	[redacted]	
Number of prior LOTs, n (%)						
≤4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]		[redacted]	[redacted]	
ECOG performance status, n (%)						
0	[redacted]	55 (33.3%)	[redacted]	[redacted]	[redacted]	[redacted]
1+	[redacted]	[redacted]		[redacted]	[redacted]	
Age, n (%)						
<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]		[redacted]	[redacted]	
Gender, n (%)						
Male	[redacted]	96 (58.2%)	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	69 (41.8%)		[redacted]	[redacted]	
Prior autologous stem cell transplantation, n (%)						
Yes	[redacted]	135 (81.8%)	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]		[redacted]	[redacted]	
Time (years) since diagnosis, n (%)						
<6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 years	[redacted]	[redacted]		[redacted]	[redacted]	
Average duration of prior lines of therapy (months), n (%)						
<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 to 14	[redacted]	[redacted]		[redacted]	[redacted]	
≥15	[redacted]	[redacted]		[redacted]	[redacted]	
Haemoglobin, n (%)						
<12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12+	[redacted]	[redacted]		[redacted]	[redacted]	
LDH, n (%)						
<280	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>280	[redacted]	[redacted]		[redacted]	[redacted]	
Creatinine clearance, n (%)						
<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-<90	[redacted]	[redacted]		[redacted]	[redacted]	

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90+	[redacted]	[redacted]		[redacted]	[redacted]	
MM type, n (%)						
IgG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-IgG	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
White	[redacted]	134 (81.2%)	[redacted]	[redacted]	[redacted]	[redacted]
Other/not reported	[redacted]	[redacted]		[redacted]	[redacted]	
Cytogenetic risk, n (%)						
Standard risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
EMD, n (%)						
Yes	[redacted]	28 (17%)	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	137 (83%)		[redacted]	[redacted]	

Abbreviations: ATT: average treatment effect for the treated; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; SMD: standardised mean difference.

Figure 6. SMDs between MonumenTAL-1 (pooled, 10:90 weighted Cohort A+C) and MajesTEC-1 cohorts, before and after adjustment

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

Figure 7. Distribution of PSs before weighting for patients in MonumenTAL-1 (pooled, 10:90 weighted Cohort A+C) and MajesTEC-1 cohort

Abbreviations: PS: propensity score

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Figure 8. Distribution of PSs after weighting for patients in MonumenTAL-1 (pooled, 10:90 weighted Cohort A+C) and MajesTEC-1 cohort

Abbreviations: PS: propensity score.

Pooled, unweighted Cohort A+C

SMDs calculated before and after ATT weighting are presented in Table 16 and Figure 9, while histograms of PSs before and after weighting are depicted in Figure 10 and Figure 11. As presented in Table 16 and Figure 9, similar to the ITC conducted between MonumenTAL-1 (Cohort C) and MajesTEC-1 in the Company Submission (Section 2.10.3), 15 of 17 prognostic variables adjusted for had an SMD ≤ ±0.2 prior to adjustment, suggesting there is a high level of alignment in the baseline characteristics of patients between the two cohorts (MonumenTAL-1 [pooled, unweighted A+C] and MajesTEC-1).

Following the adjustment for the 17 variables, none of the variables had an SMD above the threshold of 0.2, indicating that the adjustment process successfully balanced characteristics between studies (see Table 16). These alignments between the populations are also evident in the SMD plot in Figure 9 and histograms of the PSs, as shown in Figure 11.

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Table 16. SMD for unadjusted and adjusted differences between MonumenTAL-1 (pooled, unweighted Cohort A+C) and MajesTEC-1 cohort

	Before adjustment			After adjustment		
	Talquetamab	Teclistamab	SMD	Talquetamab	Teclistamab	SMD
N	297	165	-	297	165	-
Refractory status, n (%)						
≤ double refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triple refractory	[redacted]	[redacted]		[redacted]	[redacted]	
Quad refractory	[redacted]	[redacted]		[redacted]	[redacted]	
≥ Penta refractory	[redacted]	[redacted]		[redacted]	[redacted]	
ISS						
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]		[redacted]	[redacted]	
III	[redacted]	20 (12.1)		[redacted]	[redacted]	
Time to progression on prior therapy						
<3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]		[redacted]	[redacted]	
Number of prior LOTs, n (%)						
≤4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]		[redacted]	[redacted]	
ECOG performance status, n (%)						
0	[redacted]	55 (33.3)	[redacted]	[redacted]	[redacted]	[redacted]
1+	[redacted]	[redacted]		[redacted]	[redacted]	
Age, n (%)						
<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]		[redacted]	[redacted]	
Gender, n (%)						
Male	[redacted]	96 (58.2)	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	69 (41.8)		[redacted]	[redacted]	
Prior autologous stem cell transplantation, n (%)						
Yes	[redacted]	135 (81.8)	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]		[redacted]	[redacted]	

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Time (years) since diagnosis, n (%)						
<6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 years	[redacted]	[redacted]		[redacted]	[redacted]	
Average duration of prior lines of therapy (months), n (%)						
<10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 to 14	[redacted]	[redacted]		[redacted]	[redacted]	
≥15	[redacted]	[redacted]		[redacted]	[redacted]	
Haemoglobin, n (%)						
<12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12+	[redacted]	[redacted]		[redacted]	[redacted]	
LDH, n (%)						
<280	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>280	[redacted]	[redacted]		[redacted]	[redacted]	
Creatinine clearance, n (%)						
<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-<90	[redacted]	[redacted]		[redacted]	[redacted]	
90+	[redacted]	[redacted]		[redacted]	[redacted]	
MM type, n (%)						
IgG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-IgG	[redacted]	[redacted]		[redacted]	[redacted]	
Race, n (%)						
White	[redacted]	134 (81.2)	[redacted]	[redacted]	[redacted]	[redacted]
Other/not reported	[redacted]	[redacted]		[redacted]	[redacted]	
Cytogenetic risk, n (%)						
Standard risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
EMD, n (%)						
Yes	[redacted]	28 (17.0)	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	137 (83.0)		[redacted]	[redacted]	

Abbreviations: ATT: average treatment effect for the treated; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: line of treatment; MM: multiple myeloma; SMD: standardised mean difference.

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Figure 9. SMDs between MonumenTAL-1 (pooled, unweighted Cohort A+C) and MajesTEC-1 cohorts, before and after adjustment

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

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Figure 10. Distribution of PSs before weighting for patients in MonumenTAL-1 (pooled, unweighted Cohort A+C) and MajesTEC-1 cohort

Abbreviations: PS: propensity score

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Figure 11. Distribution of PSs after weighting for patients in MonumenTAL-1 (pooled, unweighted Cohort A+C) and MajesTEC-1 cohort

Abbreviations: PS: propensity score.

Additional results

The OS KM curve following subsequent treatment adjustment (including both subsequent talquetamab and teclistamab) for talquetamab (pooled, 10:90 weighted Cohort A+C) alongside the ATT-adjusted KM curves for teclistamab are presented in Figure 12. The PFS and TTD KM curves for talquetamab (pooled, 10:90 weighted Cohort A+C) alongside the ATT-adjusted KM curves for teclistamab are presented in Figure 13 and Figure 14, respectively.

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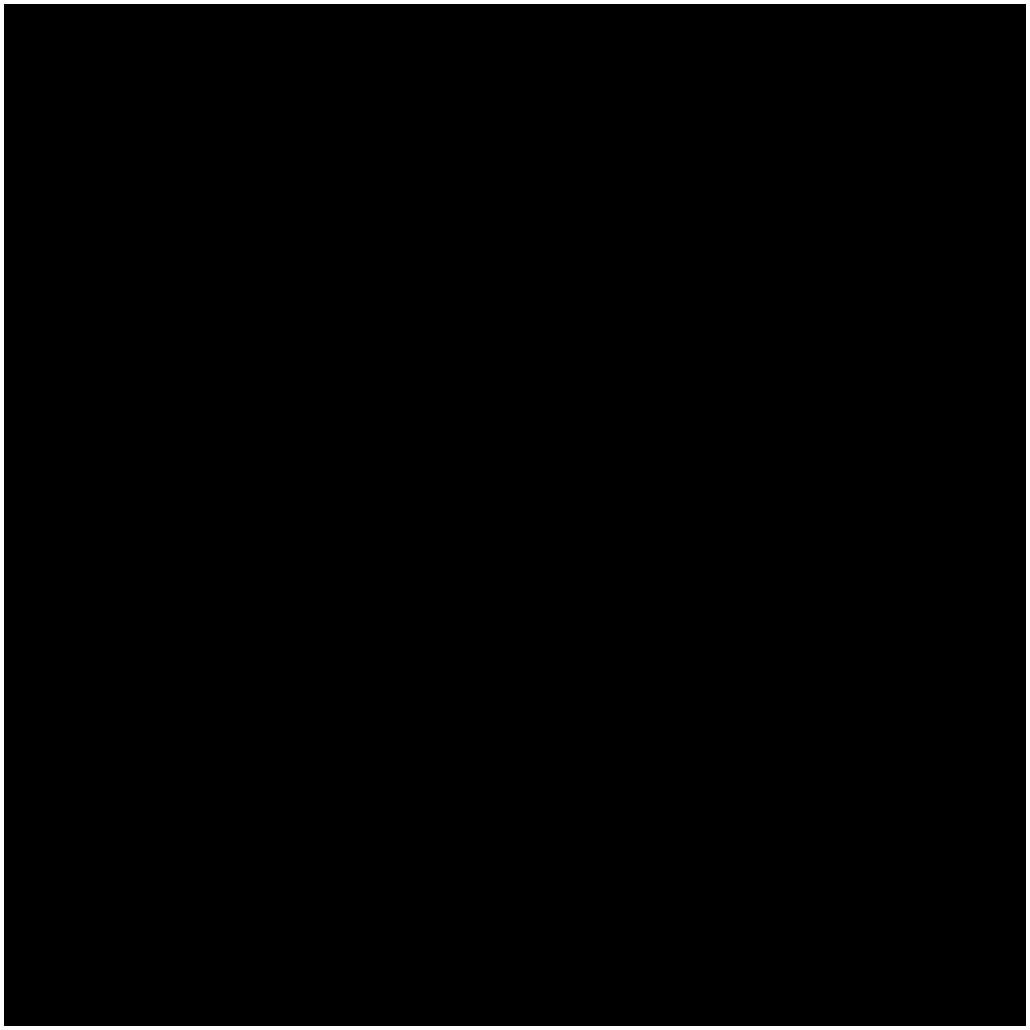
Figure 12. Subsequent-treatment adjusted OS KM curves for talquetamab (pooled, 10:90 weighted Cohort A+C) and teclistamab (after ATT weighting; post-subsequent treatment adjustment)



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

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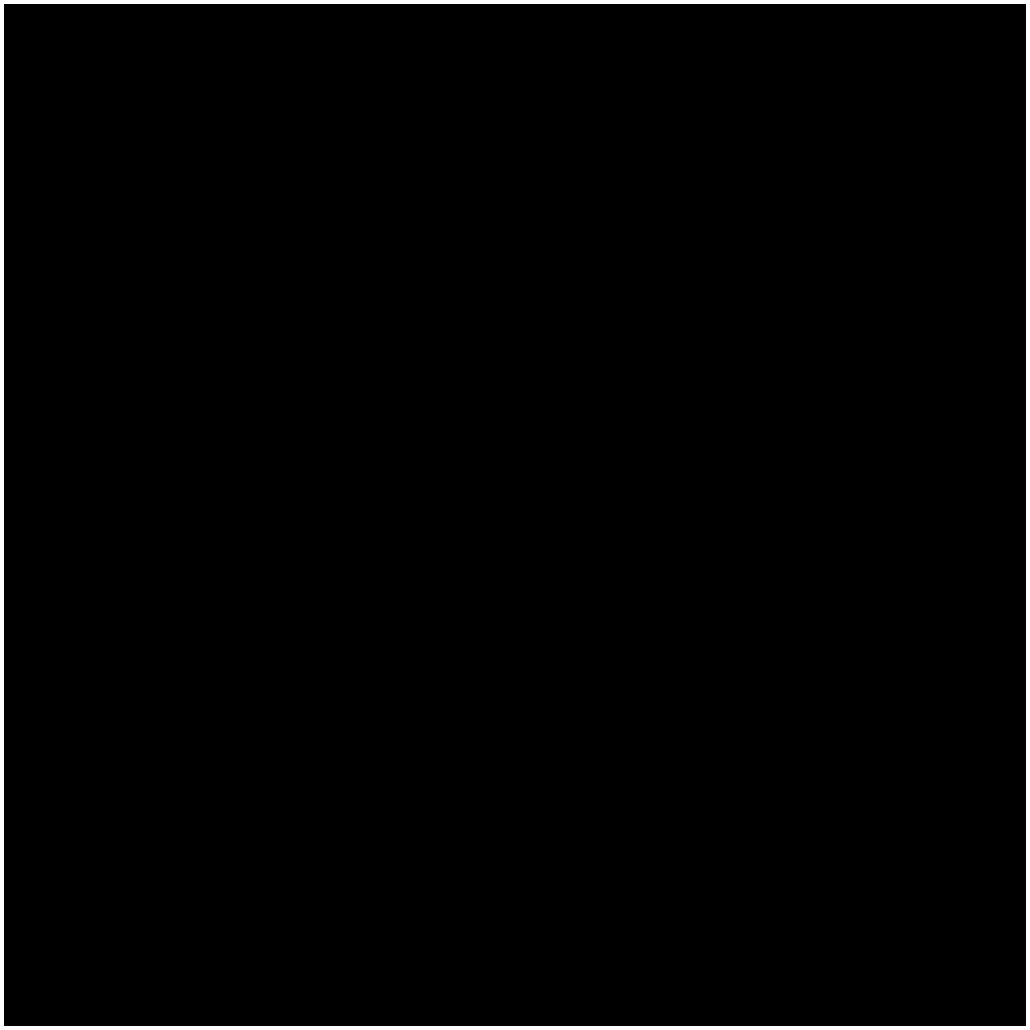
Figure 13. PFS KM curves for talquetamab (pooled, 10:90 weighted Cohort A+C) and teclistamab (after ATT weighting)



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

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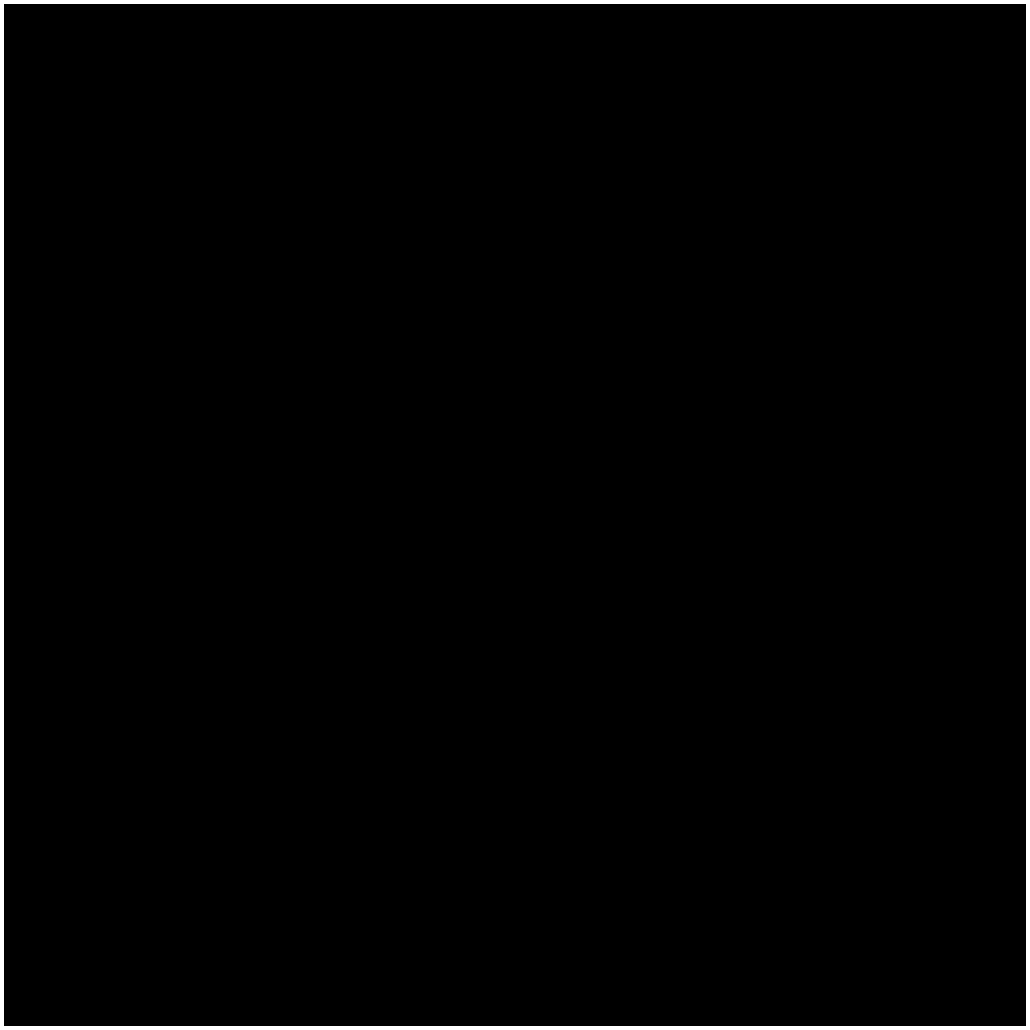
Figure 14. TTD KM curves for talquetamab (pooled, 10:90 weighted Cohort A+C) and teclistamab (after ATT weighting)



Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; TTD: time to treatment discontinuation.

The PFS, OS and TTD KM curves for talquetamab (pooled, unweighted Cohort A+C) alongside the ATT-adjusted KM curves for teclistamab are presented in Figure 15, Figure 16 and Figure 17, respectively.

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Figure 15. PFS KM curves for talquetamab (pooled, unweighted Cohort A+C after ATT weighting) and teclistamab

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

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Figure 16. OS KM curves for talquetamab (pooled, unweighted Cohort A+C) and teclistamab (ATT-weighted and post-subsequent treatment adjustment)

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; OS: overall survival.

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Figure 17. TTD KM curves for talquetamab (pooled, unweighted Cohort A+C after ATT weighting) and teclistamab

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; KM: Kaplan-Meier; TTD: time to discontinuation.

Appendix 5. Additional results from COVID-19 censored ITC analyses (Comment 2a)

A summary of the results from the COVID-19 censored ITC analyses of talquetamab versus teclistamab, based on the trial data for patients in MonumenTAL-1 and patients in the MajesTEC-1 trial are presented in the response to Comment 2a. Further results from the COVID-19 censored ITC analyses are presented in the appendix below.

MonumenTAL-1 (Cohort C) vs. MajesTEC-1 COVID-19 censored ITCs

Results: COVID-19 uncensored results for MonumenTAL-1 Cohort C and MajesTEC-1 (ATT + subsequent treatment adjusted)

The OS KM curves without COVID-19 censoring for the comparison of talquetamab (Cohort C) and teclistamab (after ATT weighting) with subsequent treatment adjustment are presented in Figure 18.

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Figure 18. OS KM curves for talquetamab and ATT-weighted teclistamab (without COVID-19 censoring) following subsequent treatment adjustment to reflect UK clinical practice, including subsequent teclistamab and talquetamab

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

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Figure 19. Log-cumulative hazard plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and without COVID-19 censoring (ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

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Figure 20. Schoenfeld residual plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and without COVID-19 censoring (ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

Results: COVID-19 base case censoring approach (censor all patients with COVID-related deaths who did not progress while on treatment and had a CR+ as the best response before death) for MonumenTAL-1 Cohort C and MajesTEC-1

The KM curves for OS after censoring for patients with COVID-related deaths using the base case approach i.e., censoring only the patients with COVID-related deaths who did not progress while on treatment and had a CR+ as the best response before death, and subsequent treatment adjustment are presented in Figure 21 for the ATT-adjusted analyses.

A log-cumulative hazard plot for talquetamab and teclistamab post two-stage adjustment and COVID-19 base case censoring approach is presented in Figure 22, and a Schoenfeld residual plot is presented in Figure 23. For OS post-adjustment and COVID-19 censoring (base case), the log cumulative plot is predominantly parallel (Figure 22). The Schoenfeld residual plot is horizontal with a p-value >0.05, providing no evidence that the PH assumption should be rejected (Figure 23).

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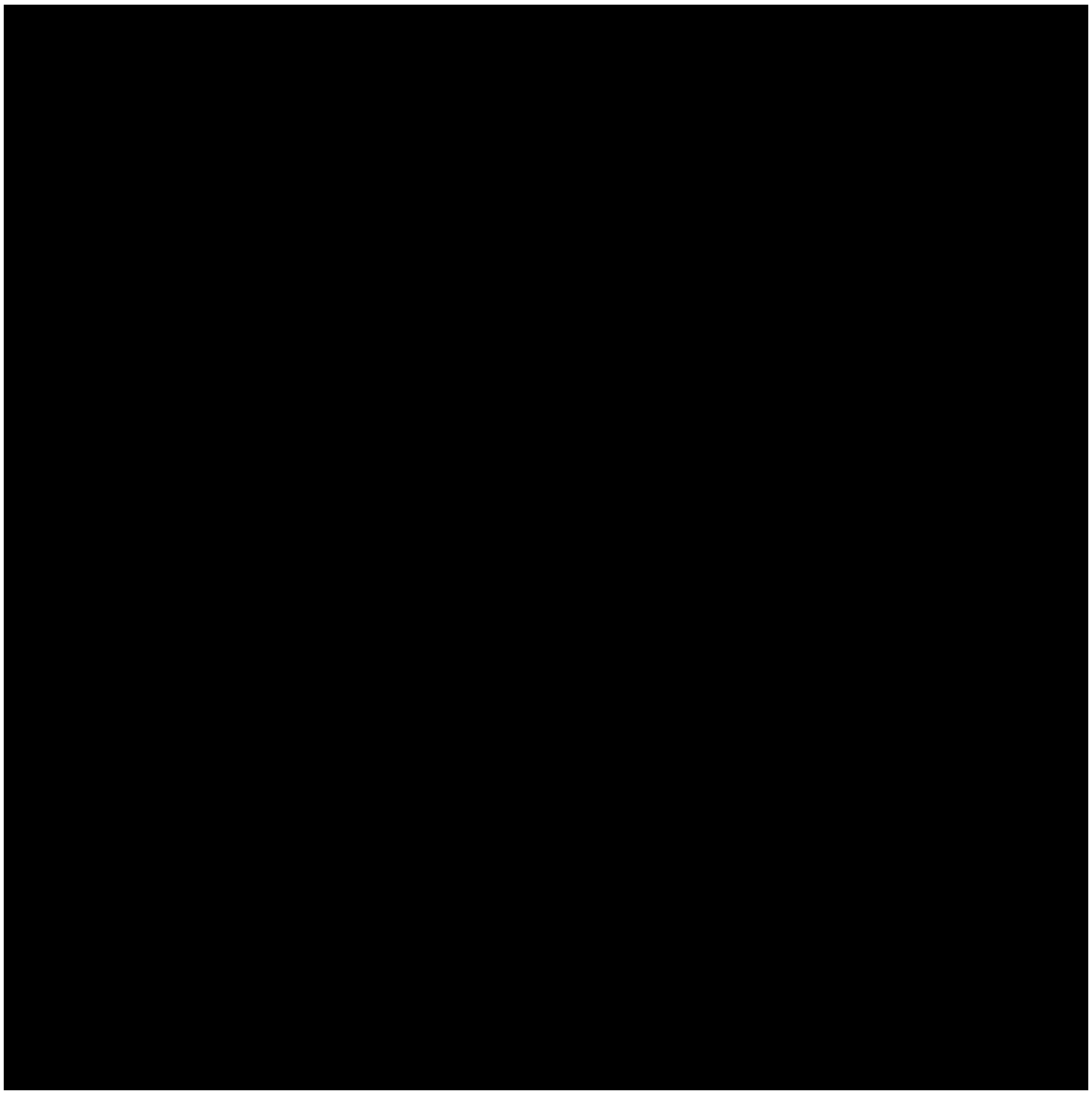
Figure 21. COVID-19 related death censored OS KM curves for talquetamab (MonumenTAL-1 Cohort C) and teclistamab (base case approach; ATT-adjusted analysis, incorporating subsequent treatment adjustment)



Abbreviations: CI: confidence interval; CR+: complete response or better; HR: hazard ratio; KM: Kaplan-Meier; NE: not evaluable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

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Figure 22. Log-cumulative hazard plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and COVID-19 censoring (base case approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

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Figure 23. Schoenfeld residual plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and COVID-19 censoring (base case approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

Results: COVID-19 alternative censoring approach (censoring all patients with COVID-related deaths) results for MonumenTAL-1 Cohort C and MajesTEC-1

The KM curves for OS after censoring for patients with COVID-related deaths using the alternative approach i.e., censoring all patients with COVID-related deaths, are presented in Figure 24 for the ATT-adjusted analyses (including subsequent treatment adjustment).

A log-cumulative hazard plot for talquetamab and teclistamab post two-stage adjustment and COVID-19 alternative censoring approach is presented in Figure 25, and a Schoenfeld residual plot is presented in Figure 26. For OS post-adjustment and COVID-19 censoring (alternative approach), the log cumulative plot is predominantly parallel (Figure 25). The Schoenfeld residual plot is horizontal with a p-value >0.05, providing no evidence that the PH assumption should be rejected (Figure 26).

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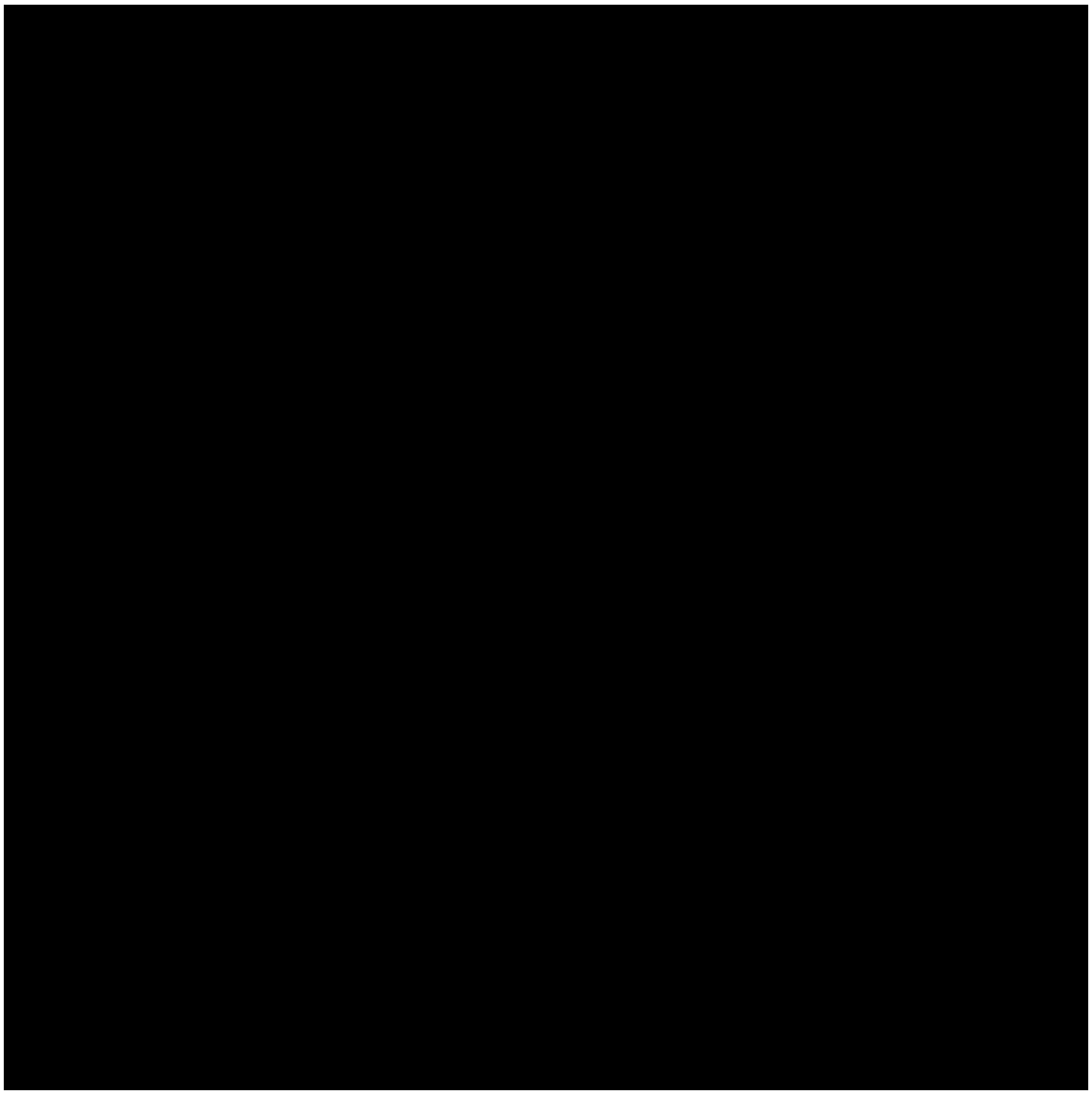
Figure 24. COVID-19 related death censored OS KM curves for talquetamab (MonumenTAL-1 Cohort C) and teclistamab (alternative approach; ATT-adjusted analysis, incorporating subsequent treatment adjustment)



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

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Figure 25. Log-cumulative hazard plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and COVID-19 censoring (alternative approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

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Figure 26. Schoenfeld residual plot OS for talquetamab (MonumenTAL-1 Cohort C) and teclistamab, post two-stage adjustment and COVID-19 censoring (alternative approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

MonumenTAL-1 Cohort A+C (pooled, 10:90 weighted) vs. MajesTEC-1 COVID-censored ITCs

Results: COVID-19 uncensored results for MonumenTAL-1 Cohort A+C (pooled, 10:90 weighted) and MajesTEC-1 (ATT + subsequent treatment adjusted)

The uncensored OS KM curves for the comparison of subsequent treatment adjusted talquetamab (pooled, 10:90 weighted Cohort A+C) and teclistamab after ATT weighting is presented in Figure 27.

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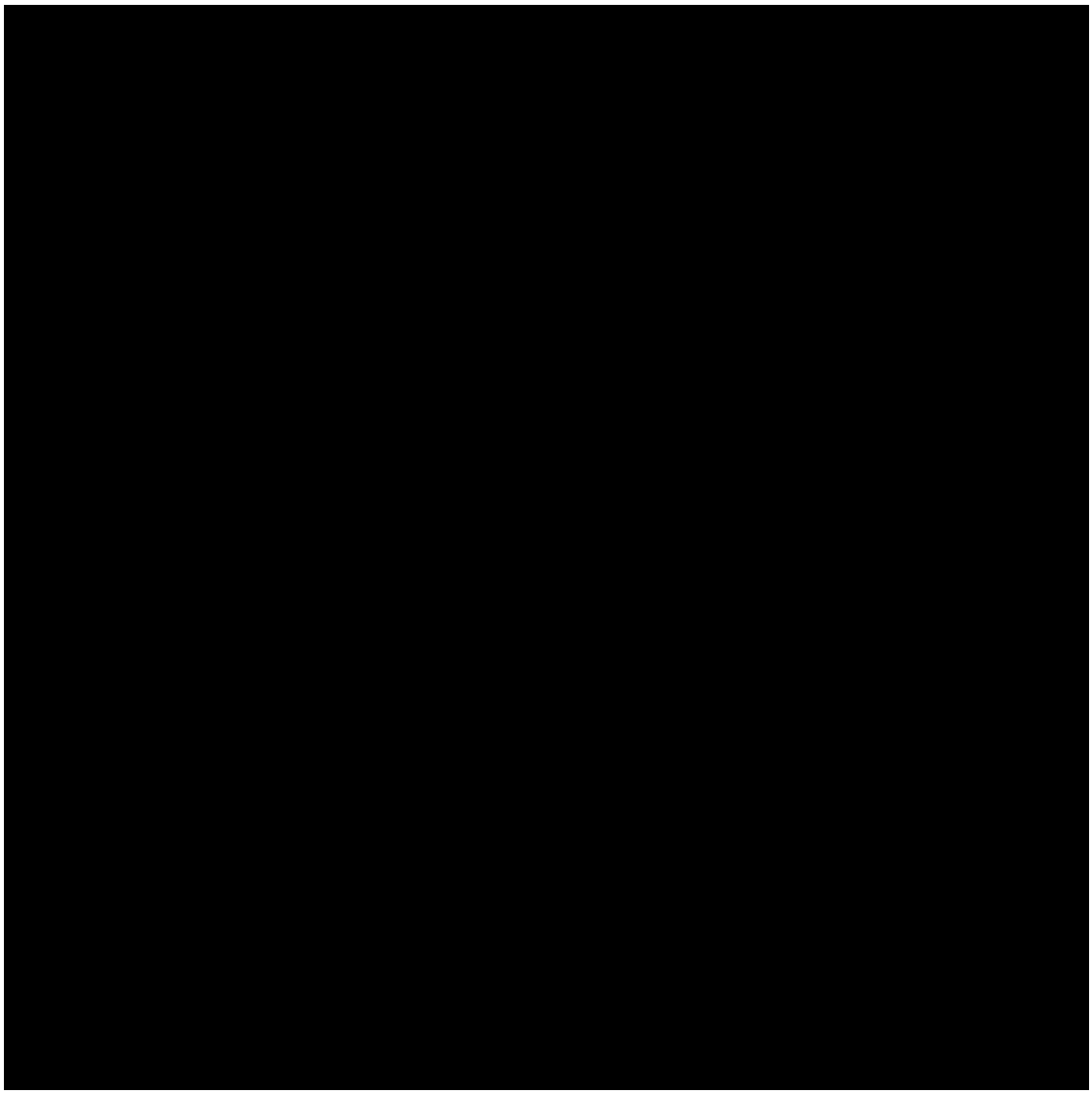
Figure 27. OS KM curves for talquetamab (pooled 10:90 weighted, Cohort A+C) and teclistamab (following ATT weighting) without COVID-19 censoring and including subsequent treatment adjustment



Abbreviations: CI: confidence interval; HR: hazard ratio; IRC: independent review Committee; KM: Kaplan-Meier; NE: not evaluable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

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Results: COVID-19 censoring base case approach (censor all patients with COVID-related deaths who did not progress while on treatment and had a CR+ as the best response before death) for MonumenTAL-1 Cohort A+C (pooled, 10:90 weighted) and MajesTEC-1

The KM curves for OS for the pooled, 10:90 weighted, Cohort A+C population after censoring for patients with COVID-related deaths using the base case approach are presented in Figure 28 for the ATT-adjusted analyses, following subsequent treatment adjustment. A log-cumulative hazard plot for talquetamab (pooled, 10%: 90% weighted Cohorts A+C) and teclistamab post two-stage adjustment and base case COVID-19 censoring is presented in Figure 29, and a Schoenfeld residual plot is presented in Figure 30. For OS post-adjustment and COVID-19 censoring (base case approach), the log cumulative plot is predominantly parallel (Figure 29). The Schoenfeld residual plot is horizontal with a p-value >0.05, providing no evidence that the PH assumption should be rejected (Figure 30).

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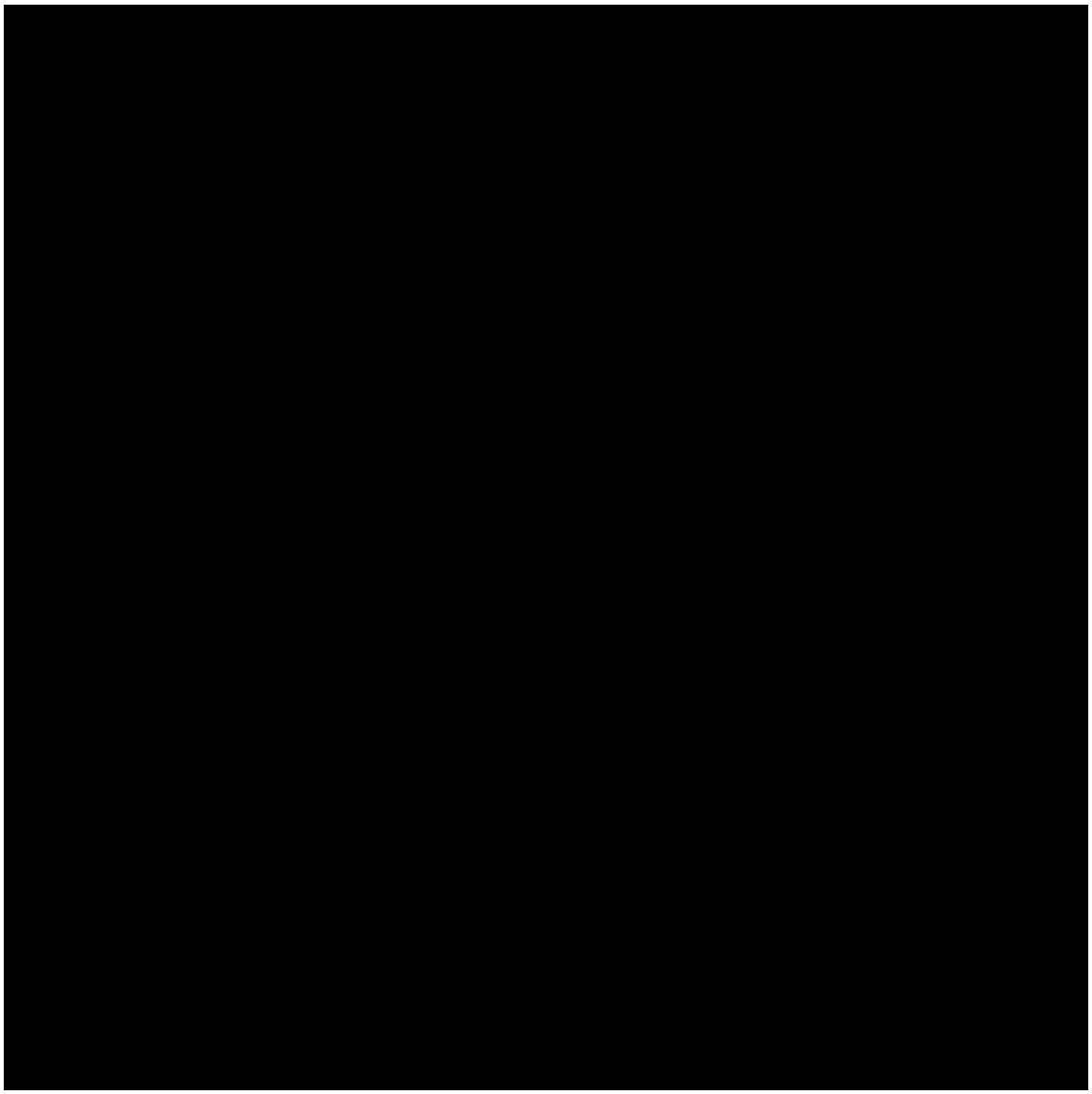
Figure 28. COVID-related death censored OS KM curves for talquetamab (pooled, 10:90 weighted, Cohort A+C) and teclistamab (base case approach; ATT-adjusted analysis, following subsequent treatment adjustment)



Abbreviations: CI: confidence interval; CR+: complete response or better; HR: hazard ratio; KM: Kaplan-Meier; NE: not evaluable; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

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Figure 29. Log-cumulative hazard plot OS for talquetamab (pooled, 10:90 weighted, MonumenTAL-1 Cohort A+C) and teclistamab, post two-stage adjustment and COVID-19 censoring (base case approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

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Figure 30. Schoenfeld residual plot OS for talquetamab (pooled, 10:90 weighted, MonumenTAL-1 Cohort A+C) and teclistamab, post two-stage adjustment and COVID-19 censoring (base case approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

Results: COVID-19 alternative censoring approach (censoring all patients with COVID-related deaths) results for MonumenTAL-1 Cohort A+C (pooled, 10:90 weighted) and MajesTEC-1

The KM curves for OS for the pooled, 10:90 weighted, Cohort A+C population after censoring for patients with COVID-related deaths using the alternative approach (wherein all COVID deaths are censored) are presented in Figure 31 for the ATT-adjusted analyses, following subsequent treatment adjustment. A log-cumulative hazard plot for talquetamab (pooled, 10%: 90% weighted Cohorts A+C) and teclistamab post two-stage adjustment and COVID-19 alternative censoring approach is presented in Figure 25, and a Schoenfeld residual plot is presented in Figure 26. For OS post-adjustment and COVID-19 censoring (alternative approach), the log cumulative plot is predominantly parallel (Figure 25). The Schoenfeld residual plot is horizontal with a p-value >0.05, providing no evidence that the PH assumption should be rejected (Figure 26).

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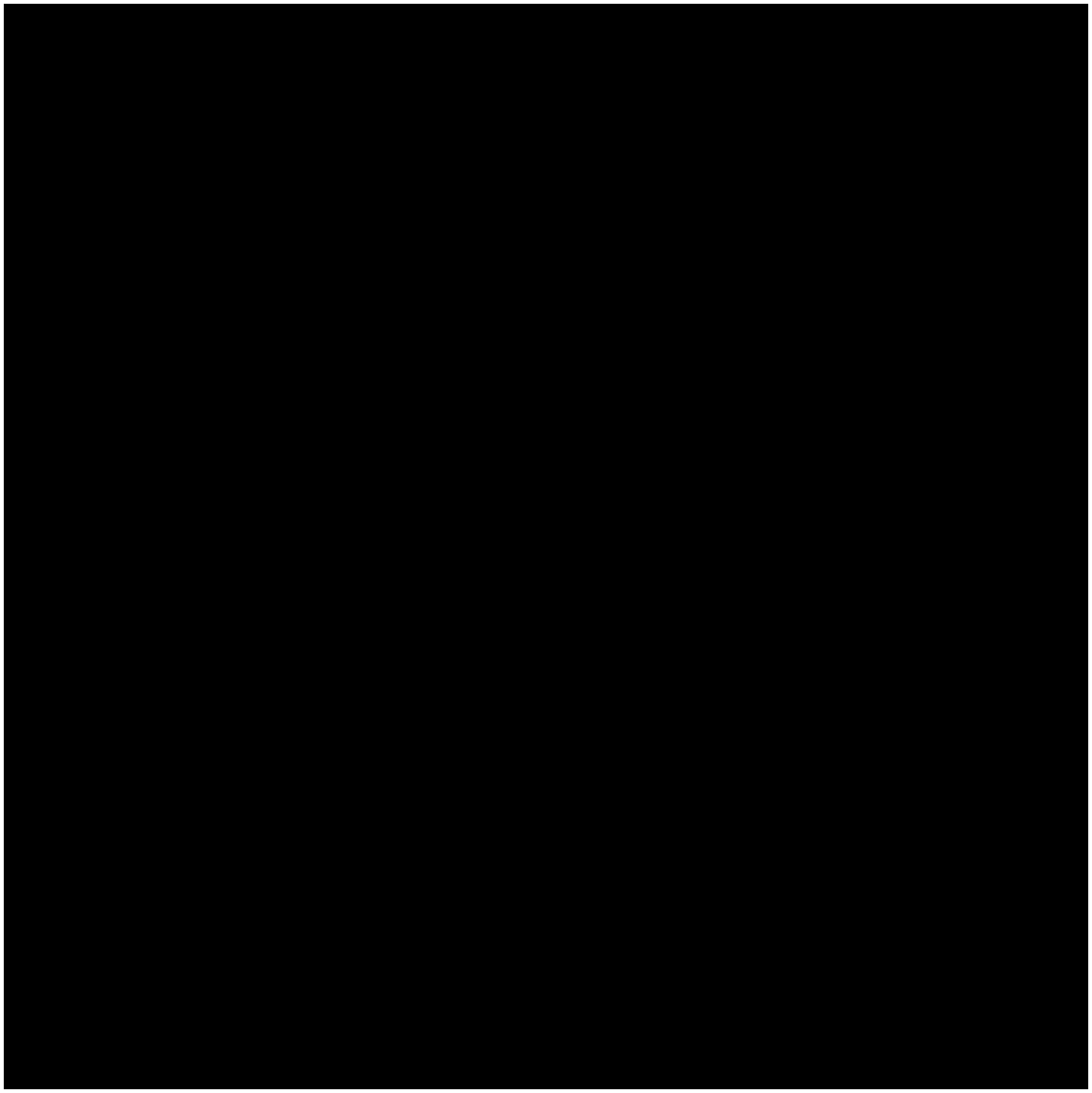
Figure 31. COVID-19 related death censored OS KM curves for talquetamab (pooled, 10:90 weighted, MonumenTAL-1 Cohort A+C) and teclistamab (alternative approach; ATT-adjusted analysis)



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

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Figure 32. Log-cumulative hazard plot OS for talquetamab (pooled, 10:90 weighted, MonumenTAL-1 Cohort A+C) and teclistamab, post two-stage adjustment and COVID-19 censoring (alternative approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

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Figure 33. Schoenfeld residual plot OS for talquetamab (pooled, 10:90 weighted, MonumenTAL-1 Cohort A+C) and teclistamab, post two-stage adjustment and COVID-19 censoring (alternative approach; ATT-adjusted analysis)

Abbreviations: ATT: average treatment effect in the treated; OS: overall survival.

Appendix 6. Additional results from ITC PFS2 analyses (Comment 2b)

Censoring rules

In the PFS2 analyses patients who are alive and for whom a second progressive disease event has not been observed are censored at the last date of follow-up.

For patients who did not initiate any subsequent therapy, those who died were also considered as having a PFS2 event. For patients who did not progress or die after the first subsequent therapy, but initiate any second subsequent therapy, they were censored at the start date of the second subsequent therapy.

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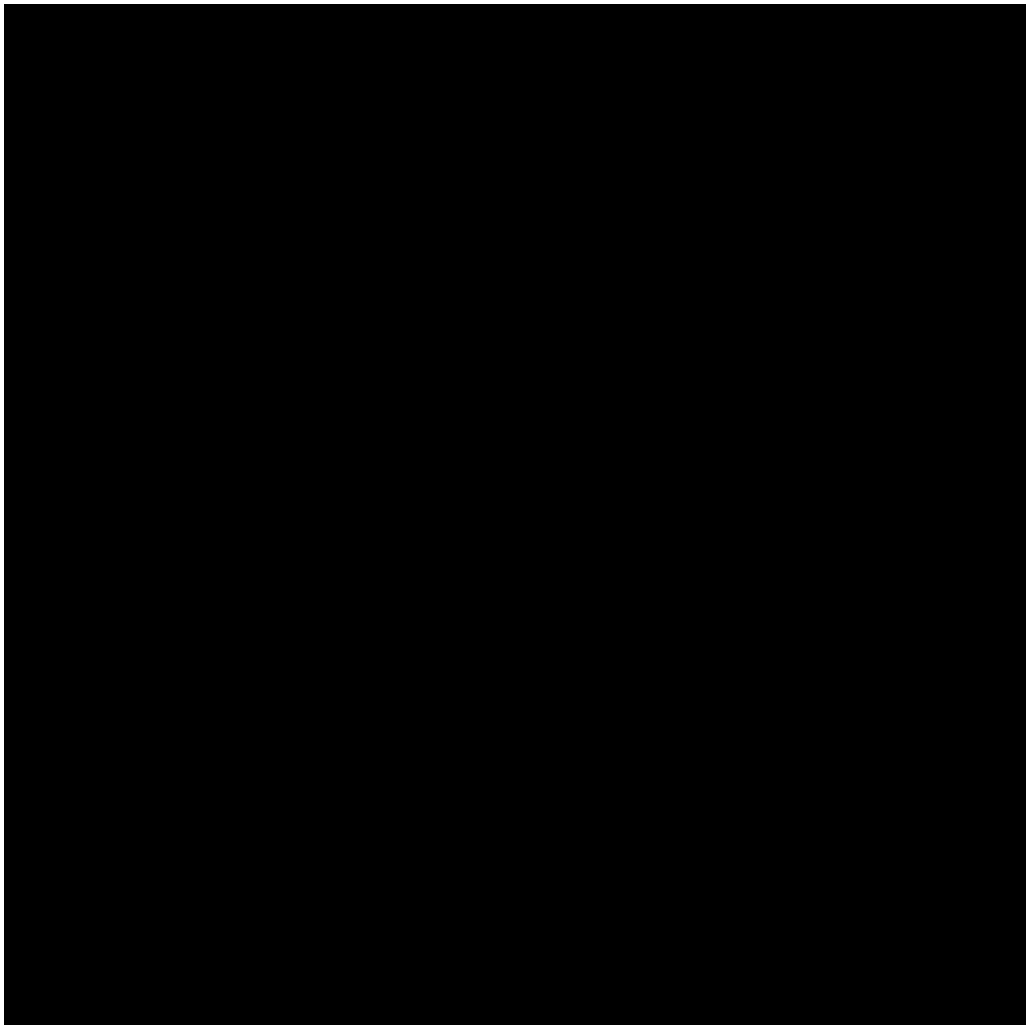
Results

The KM curves for PFS2 with the all-in two-stage adjustment (including both subsequent teclistamab treatment and subsequent talquetamab, as per the revised base case) are presented in Figure 34 (following ATT-adjustment).

Figure 34. PFS2 KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis, post-subsequent treatment adjustment; all-in)



Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; NE: not evaluable; PFS2: progression-free survival after subsequent treatment; TAL: talquetamab; TEC: teclistamab.

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Appendix 7. Additional information relating to the independent modelling scenarios (Comment 5)

The long-term PFS, TTD and OS extrapolations for talquetamab (pooled, 10:90 weighted Cohort A+C; post-subsequent treatment adjustment) are presented in

Figure 35, Figure 36 and Figure 37, respectively. The goodness-of-fit statistics for the talquetamab OS extrapolations (Cohort C, post-subsequent treatment adjustment are presented in Table 17.

Figure 35. PFS extrapolations for talquetamab (pooled, 10:90 weighted Cohort A+C; post-subsequent treatment adjustment)

Abbreviations: PFS: progression-free survival.

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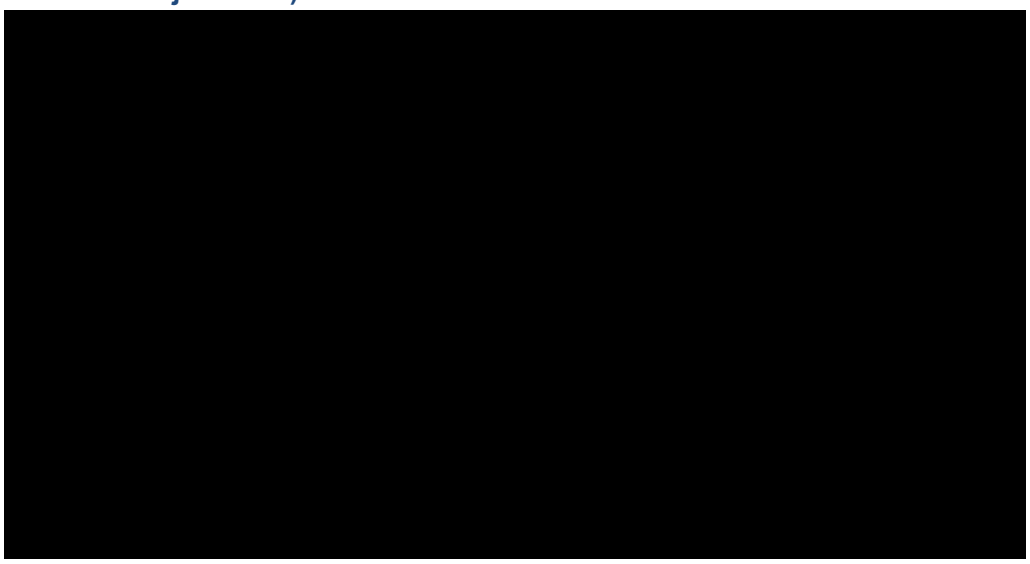
Figure 36. TTD extrapolations for talquetamab (pooled, 10:90 weighted Cohort A+C; post-subsequent treatment adjustment)



Abbreviations: TTD: time to treatment discontinuation.

Figure 37. OS extrapolations for talquetamab (pooled, 10:90 weighted Cohort A+C; post-subsequent treatment adjustment)

Abbreviations: OS: overall survival.

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Table 17. Goodness-of-fit statistics for talquetamab OS extrapolations (Cohort C; post-subsequent treatment adjustment)

Survival model	Talquetamab			
	AIC	BIC	AIC Rank	BIC Rank
Weibull	[redacted]	[redacted]	5	4
Exponential	[redacted]	[redacted]	7	5
Lognormal	[redacted]	[redacted]	2	2
Loglogistic	[redacted]	[redacted]	4	3
Gompertz	[redacted]	[redacted]	**1**	**1**
Gamma	[redacted]	[redacted]	6	6
Generalised Gamma	[redacted]	[redacted]	3	7

Footnotes: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Appendix 8. Additional results from the exploration of alternative parametric distributions in the two-stage adjustment (Comment 6)

The KM curves for OS with alternative parametric distributions in the two-stage adjustment are presented in Figure 39 to Figure 43. Results of the alternative parametric distributions indicate marginal differences in OS HR.

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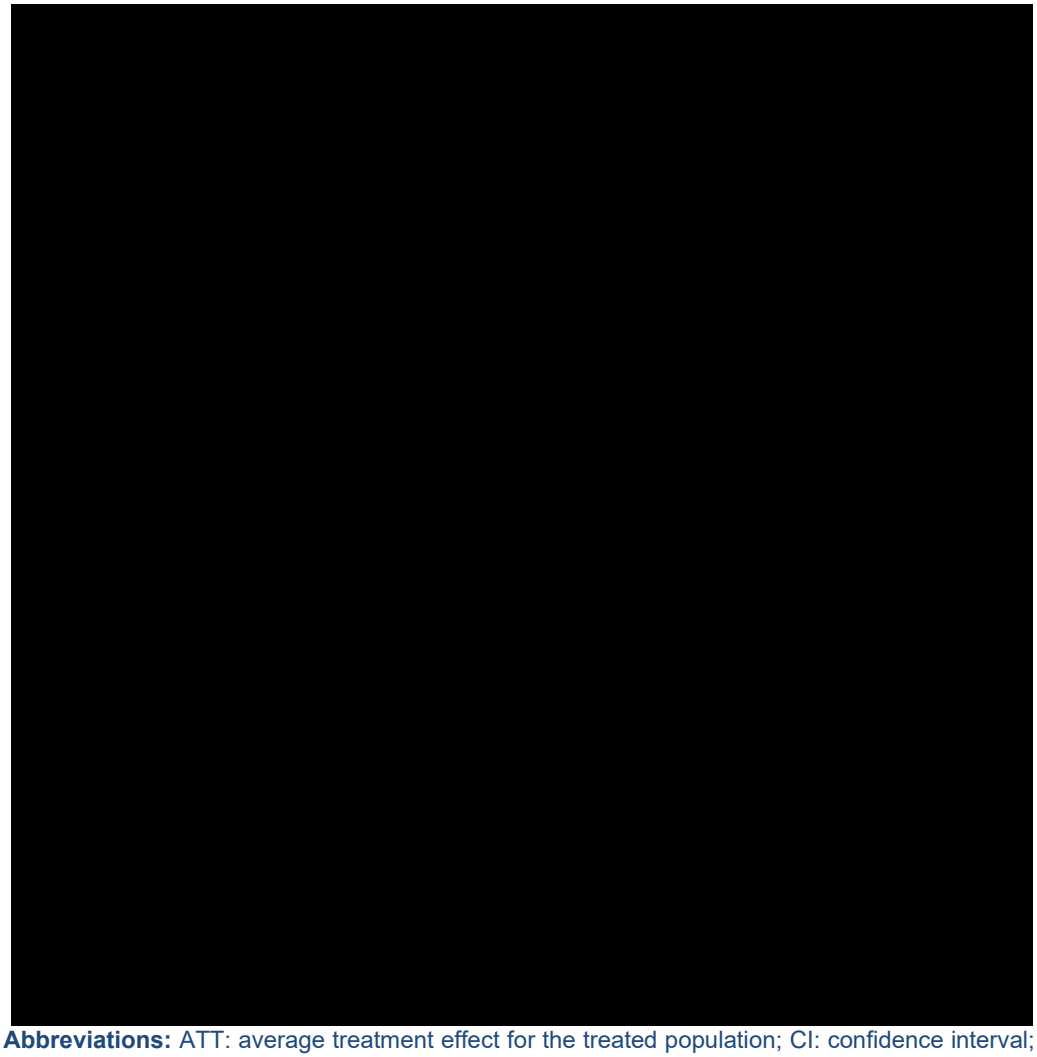
Figure 38. OS KM curves for talquetamab (Cohort C) and teclistamab (naïve)



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

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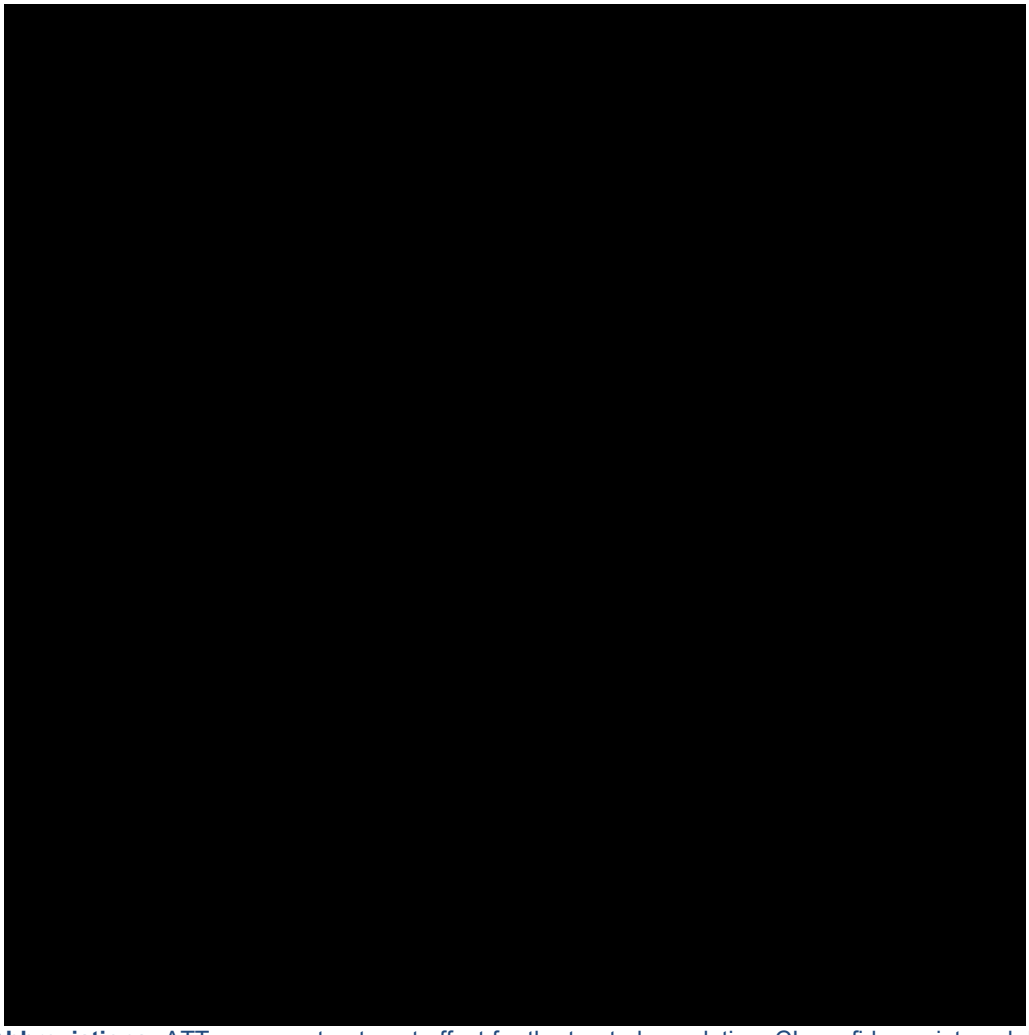
Figure 39. OS KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis; two-stage adjustment using Exponential distribution)



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

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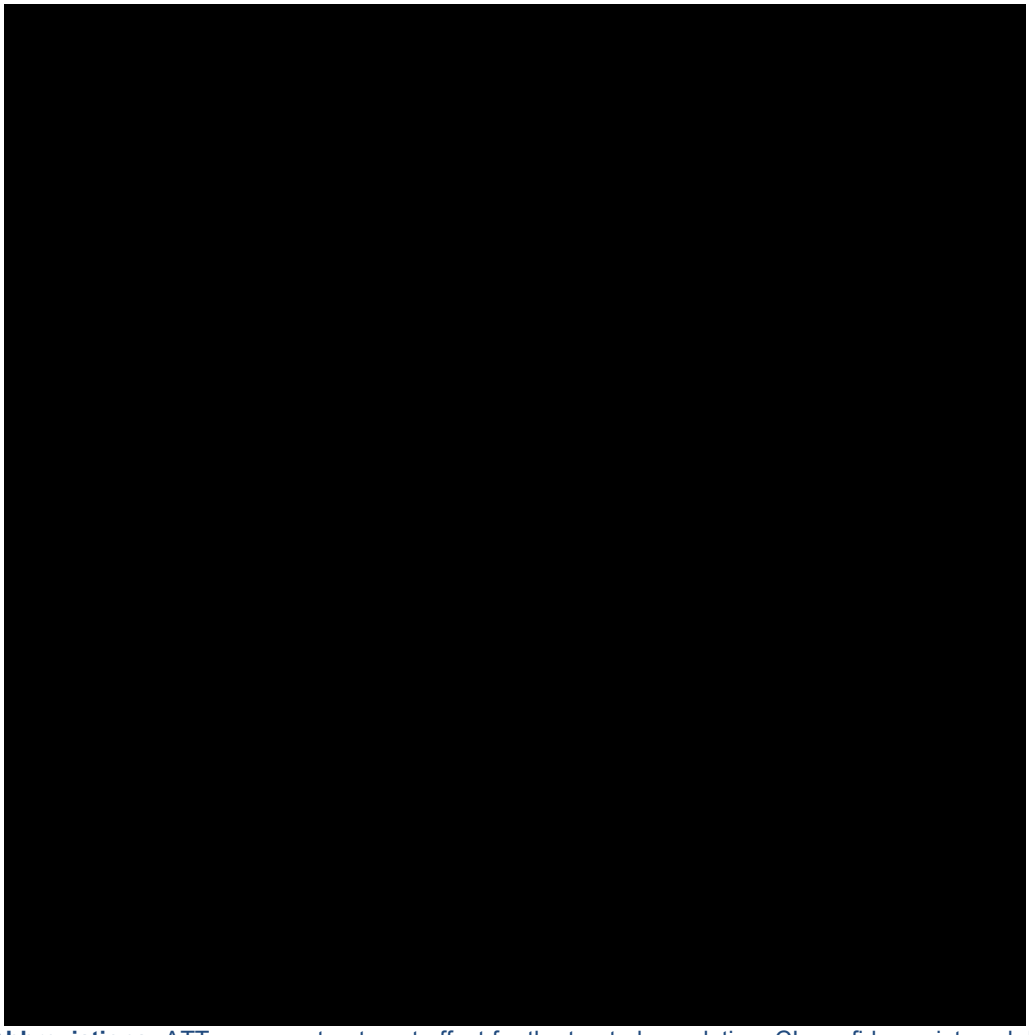
Talquetamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (ID5082)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 25th September 2025. Please submit via NICE Docs.

Figure 40. OS KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis; two-stage adjustment using Weibull distribution)



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

NICE National Institute for Health and Care Excellence

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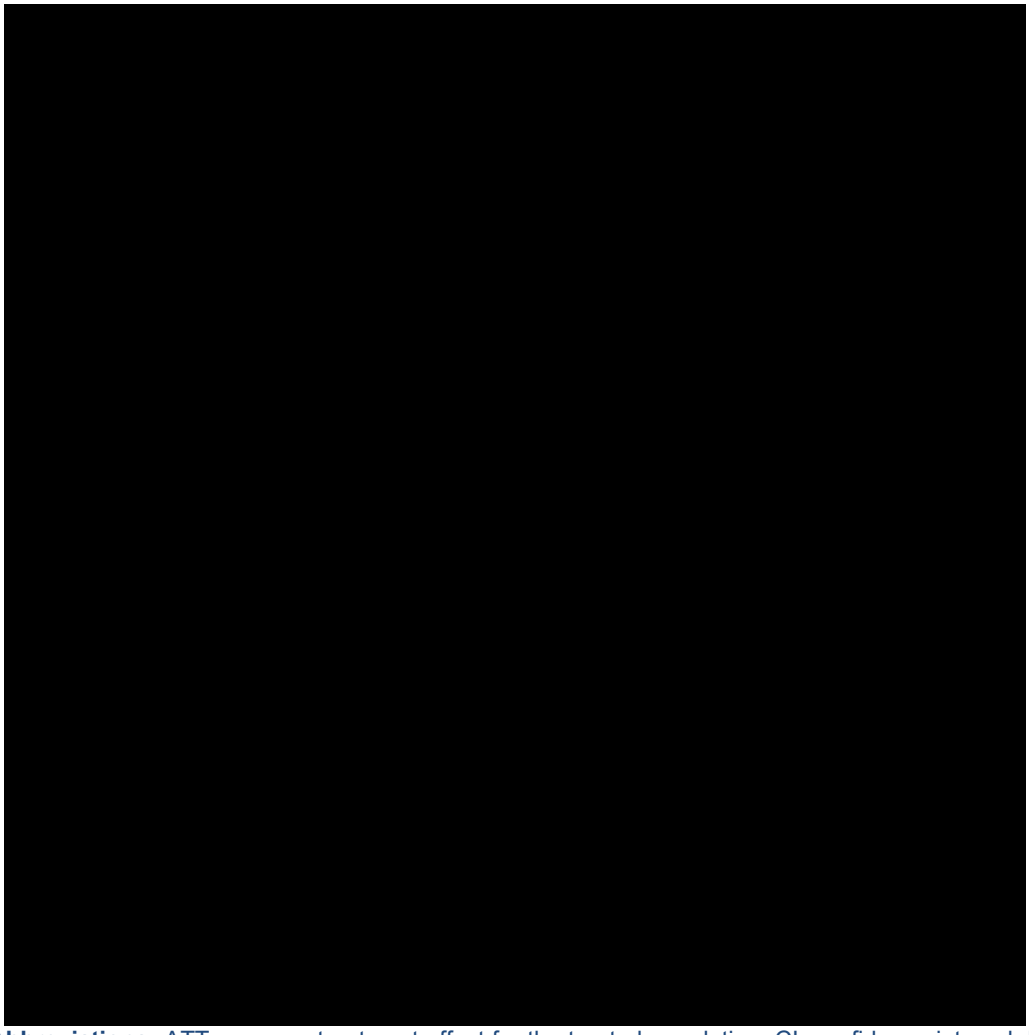
Figure 41. OS KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis; two-stage adjustment using Gamma distribution)



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

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NICE National Institute for Health and Care Excellence

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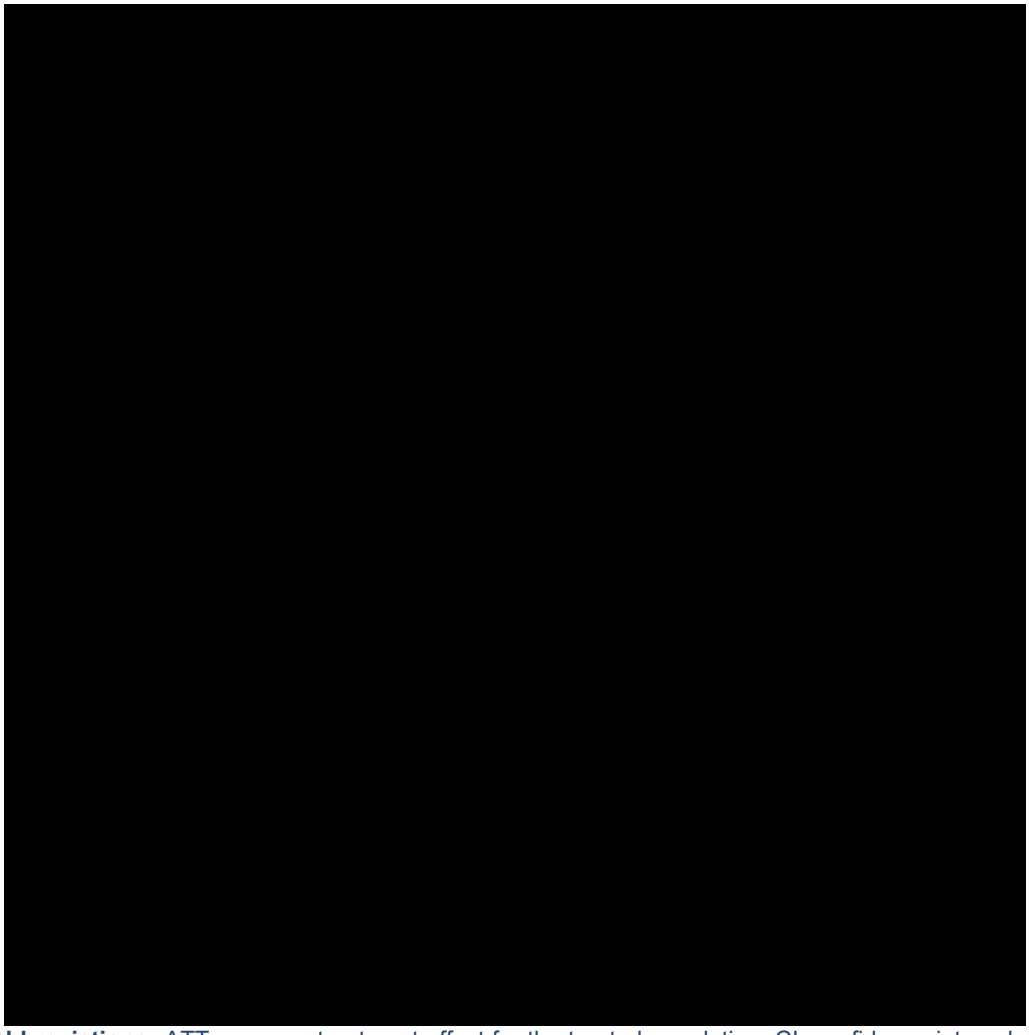
Figure 42. OS KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis; two-stage adjustment using LogLogistic distribution)



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

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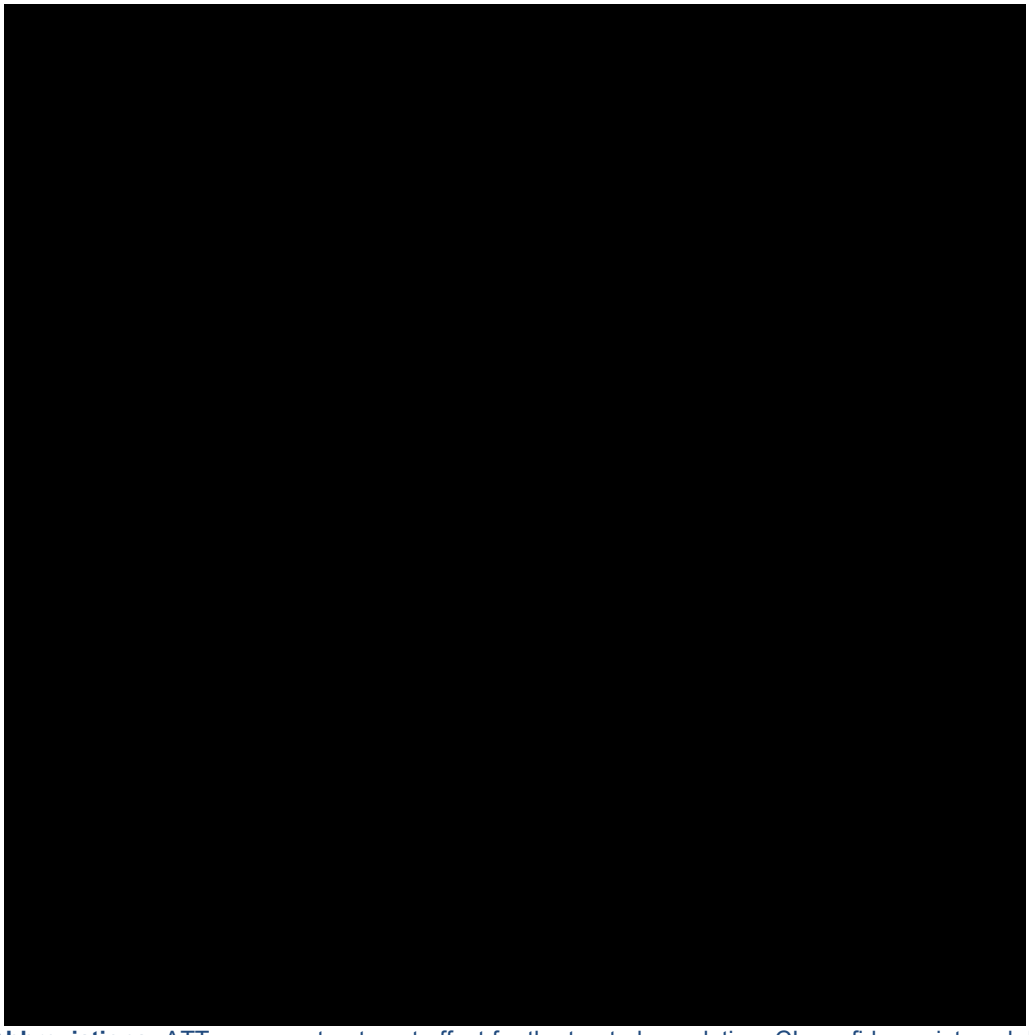
Figure 43. OS KM curves for talquetamab (Cohort C) and teclistamab (ATT-adjusted analysis; two-stage adjustment using LogNormal distribution)



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

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Myeloma Society Dr Sarah Lawless, Consultant Haematologist, Executive member UKMS Dr Neil Rabin, Consultant Haematologist and Executive Member UKMS (nominated by the company)

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	UK Myeloma Society has received an unrestricted educational grant from Janssen (£12,000 per annum). UK Myeloma Society has also received unrestricted educational grants from other pharmaceutical companies. Dr Lawless (disclosures): Advisory boards-Abbvie 2018 only, BeiGene 2023 only, BMS/Celgene 2024 Congress support BeiGene 2024, Janssen 2024 and astrazenca 2025 Speaker fees-BMS/Celegene 2024, Janssen 2023, Sanofi 2024 and Beigene 2024 **Direct – non-financial** (if you have no interests in this category, state 'None') Member of UK Myeloma Society-Invited N. Ireland representative on executive committee Member of Royal College of Pathologists My institution is site selected for the TALISMAN trial for which I am principal investigator. This is a phase II study A study to evaluate preventive treatments for talquetamab-related oral toxicity Dr Rabin (disclosures): • Janssen – advisory board, speaker fees, support to attend conferences • GSK – advisory board • Sanofi - advisory board, speaker fees • BMS (Celgene) - advisory board, speaker fees • Pfizer - advisory board, speaker fees • Menarini Stemline- advisory board, speaker fees, support to attend conferences
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Sarah Lawless and Dr Neil Rabin Nominated clinical experts

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation will prevent the access to a therapy with a novel target which is increasingly important for patients with relapsed or refractory myeloma. Talquetamab is a bi-specific antibody with an orphan receptor target GPRC5D. This is highly expressed on malignant plasma cells and keratinised tissues and very low expression on other cells making this an attractive target for patients with relapsed myeloma. The standard of care for a patient with myeloma who is triple class exposed and at 4th line is teclistamab (BCMA target) if a patient is otherwise fit to receive a bi specific antibody. Given the ever evolving pathway we now have access to a belantamab a BCMA targeting antibody drug conjugate. At 4th line if a patient is triple class exposed the current recommendation will preclude patients access a novel target which will be increasingly important for patients who receive a BCMA targeting drug at second line or earlier in the pathway. The availability of belantamab will not displace the use of teclistamab if this is the only bi specific antibody in this space for a patient who has not received a bi specific antibody.
2	Infection is one of the biggest causes of morbidity and mortality in patients with myeloma. By the time a patient reaches 4th line and is triple class exposed many patients will have issues with infection and a significant number may already require IVIg to help mitigate risk of infection We know that BCMA bi specific antibodies carry a high risk of infection and this risk does not plateau. We see that per month there is a 3% risk of grade ≥3 infection in patients receiving BCMA bi specific antibodies (teclistamab, but also elranatamab and linvoseltamab i.e. BCMA specific effect). Whereas the overall risk of all grade infection and grade ≥3 infection is substantially lower (grade ≥3 infection is 50% lower at 1.5% per month) for talquetamab There is an unmet need for patients at high risk of infection Talquetamab is highly efficacious in triple class exposed patients and has a much lower rate of more serious infection therefore likely reducing the demand on unscheduled care and hospital resources compared to bi specific antibodies and reducing morbidity for patients and it is possible that this could also contribute to the IS advantage
3	We note that this recommendation called in to question the OS benefit provided in the ITC. However if we look at the follow up from MajesTEC 1 (teclistamab) the overall survival at 30 months was 41.9% whereas for MonumenTAL 1 (talquetamab) overall survival at 36 months was 60.8% While we cannot perform cross trial comparisons the ITC demonstrated OS when controlling for 17 variables. The committee raised concern regarding impact of covid deaths in MajesTEC1, we await covid censorship but I would point out that the majority of deaths are due to progressive disease.
4	The committee raised concern regarding the OS benefit derived from the ITC However the novel mechanism of action of talquetamab sets this drug apart and may account for the differences we observed. We know from clinical experience that patients who fail a BCMA bi specific in the early months due to progressive disease are a challenging group of patients and often have a much more aggressive clinical course compared to those who have an initial response and relapse later. This may account for the earlier separation of the curves Reviewing the trial literature a higher proportion of patients progressed in the first few months of teclistamab in MajesTEC1 than talquetamab in MonumenTAL 1

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	A
5	The committee highlighted the regression analysis by Cartier 2015 and Eketal 2021 however these methods pre date the use of bispecific antibodies and caution should be applied when using regression analysis not studied with therapies with a novel mechanism of action
6	Note the committee wished to review modelling for cohort A-weekly dosing However biweekly dosing is likely be to more suitable for both patient experience and day ward capacity and in theory this result in less T cell exhaustion with bi weekly dosing rather than weekly.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK

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Disclosure

Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]

Please state:

- the name of the company
- the amount
- the purpose of funding including whether it related to a product mentioned in the stakeholder list
- whether it is ongoing or has ceased.

We have received funding from the drug manufacturer (Johnson & Johnson) in the last 12 months.

The table below shows the 2024 income from the relevant manufacturers and other pharmaceutical companies. Funding is received for a range of purposes and activities namely core grants, project specific work, honoraria, or sponsorship events. The funding received from the pharmaceutical industry in 2024 was approximately 4% of our annual income.

	Core grant	Research / Project	Consultancy/ Honoraria	Events	Total
Akt Health Communications			240		240
Alexion Pharma UK Ltd		10000			10000
The Binding Site Ltd	25000				25000
Bristol-Myers Squibb Pharmaceuticals Ltd	10000				10,000
Gilead Sciences		19000			19,000
GlaxoSmithKline UK Limited			700		700
ITECHO Health Ltd		1500			6600
Johnson & Johnson / Janssen-Cilag Ltd	19400		200	13990	33590
Kyowa Kirin Ltd		5000			5000
Menarini Stemline UK Limited			1844	3423	5267
Merck Sharp and Dohme		15000			15000
Pfizer Limited		9391			9391
Oxford Biomedica UK Limited	5000				5000
Sebia				11192	11,192
Sanofi			720	33,990	34710
Takeda	20000		880	15389	36269
Totals	79400	59891	4584	77984	221,859

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Caroline Donoghue

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that the committee didn't consider that the taste and appetite-related side effects of talquetamab were manageable in relation to side effects caused by other treatments. Unfortunately, all myeloma treatments have side effects that impact quality of life in different ways and to varying degrees. People who are currently on talquetamab often say that the taste and appetite-related side effects do affect them, but that they are not as significant as some of the side effects they have had while on other myeloma treatments. The effects reduce over time, are manageable and not permanent like peripheral neuropathy. They also say that they can continue to be active and live their lives whilst experiencing the taste-related side effects, unlike symptoms like fatigue or increased risk of infection. A higher risk of infection means reducing social activities, avoiding crowded places, and adding additional anxiety when travelling. ***"Talquetamab did not affect my taste, but it did affect my appetite for about nine months, and I had a very dry mouth for the first six months. My mouth is still dry, but much better. I lost 7 kg in weight and spoke to a dietitian about this. For the dry mouth, I used Biotene gel and Glandosane spray, which helped a bit.*** ***My mouth is still a bit dry, but it is manageable. My appetite has been very good for the past year, and my weight is back to normal. I think the dry mouth was similar to the treatment with thalidomide, but worse than any of the other treatments I have had for the myeloma. I have been in remission for twenty-one months and have felt very well during this time. I lead a fairly active and fulfilled life, and I am very grateful to have been prescribed talquetamab treatment. The side effects are manageable and minimal compared to other treatments I have had in the past."*** ***"I did have taste changes with Tal. Initially, I found I couldn't taste anything much, although it's important to note that my olfactory sense was normal. Treatment started mid-April 2024, and only since March 2025 has my taste been returning. I found that taste buds for sugar and salt were most affected: fruits were therefore very acidic (as they truly are) without the benefit of the fructose, which one normally tastes and masks the***

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	acidity. Crisps were a laugh - salt undetectable, no taste and only the crunchiness was evident. ***It was a bit sad, but I didn't obsess over it. I am just happy that I'm alive and lucky to be on a Trial."*** ***"Regarding taste, I suddenly had an immediate and almost complete loss of taste when I was still being introduced to the drug at a lower dose. Initially, I was losing about 1 kg a week - my consultant was extremely concerned about this weight loss, in fact, more than I was, because at the time I was considerably overweight. I am now approximately 100 kg, and when I was in my 20s, I was 70 kg, which was probably my correct weight. My taste has come back partly. It is difficult to put a specific measurement, but I would say I taste things to approximately 60%. As I am able to eat normally and maintain my current weight, I try not to let loss of taste bother me too much. The side effects of my first course of treatment were more difficult to manage than those I am experiencing now. Because of its very successful effects on my cancer, I am extremely grateful to have been given the opportunity to take the drug."*** ***" My quality of life on talquetamab is much better than previous treatments. After the initial side effects of skin irritation and dryness had settled down, there were really no side effects. Everything tastes of salt, but after a while, one gets used to it. The side effects of this drug are trivial compared to all the other lines of chemotherapy I have been on."*** ***"Life is better on talquetamab than with other myeloma treatments, as the side effects are minimal. Things taste like cardboard, but I have gotten used to it. They wish to increase the time between treatments to see if my taste comes back. As the results are very promising, I would rather have no taste and have strong results"*** ***"My earlier treatments caused severe gastric problems that were quite painful. I went on to teclistamab, and the stomach issues went away, but I got serious infections (once into intensive care) because of its impact on the immune system. Talquetamab has allowed my immune system to start to recover, and I have had no infections for almost a year. The side effects have not impaired the quality of my life, and I regularly walk for well over an hour a day in the country, go to the gym twice a week and have had two holidays overseas this year as well as three UK weekends. The main impact on my taste/appetite was that food tasted bland and was hard to swallow. This improved after 4-5 months, although the taste changed (e.g. still cannot stand sweet things). We worked on making food easily digestible by using liquidisers, sauces, gravy and preparing soups. I started to regain and, as time went on, return to my normal weight (I lost weight because of hospitalisation due to an immune system deficiency and recurring infections). As the problems did not last that long and were manageable (albeit with a willing patient and diet-aware wife), the issue was relatively minor- irritating when hoping to go out or on holiday but manageable otherwise"***
2	We are concerned that the committee's request to include the data from the weekly dosing for talquetamab doesn't reflect patient preference and how the treatment would be used in clinical practice.

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	We believe most, if not all, myeloma patients would opt for the biweekly dosing for talquetamab. Therefore, the data for the biweekly dosing is most representative of clinical practice. The biweekly dosing also uses less hospital capacity and resources and would be the preferred option in clinic. To confirm this, we asked the patients in our Myeloma UK Advocacy Partner Panel, an advisory committee of lived experience patients and carers, if they were offered a new treatment for myeloma that could be given by injection under the skin weekly or biweekly (fortnightly). Which dosing schedule would they prefer and why? And if there were any other things you would consider when making this decision? All 12 patients who responded said that they would choose the biweekly dosing schedule. The reasons cited included fewer hospital visits and related travel costs, more time to recover between doses, easier to fit around life and lessened skin damage and bruising. ***"The less frequent the better as it means fewer trips to hospital, less to pay on parking and fewer interruptions to your day to day life (assuming these injections must be done at hospital)"*** ***"biweekly because skin damage will be lessened, and because it's less intrusive on their lives i.e. one less day of hospital appointments."*** ***"Limiting choices and chances to 'get away'. Yes, I know quite a few people have their treatment weekly etc, but we need to remember that the treatment for Myeloma should not take over our whole life."*** ***"Less visits to the hospital which would allow more time in between appointments to arrange work schedules and social events and therefore not so tied to your treatment plan. Also, cuts down on travel expenses. More chance to recover from any side effects."."*** Their decision would also be influenced by efficacy, side effects, level of supportive treatments required (e.g. frequency of dexamethasone) and if the treatment could be self-administered. ***"factors affecting this decision would be the delivery method (a self-administered sub cut weekly is easier to manage than a bi-weekly inpatient delivery), differing side effects or AE risk for the two options and the big one would be the efficacy of each regime***
3	We are concerned that the economic model doesn't fully capture the need for and the benefit of the novel way talquetamab targets myeloma cells. Talquetamab is the only treatment for myeloma that targets myeloma cells via the GPRC5D protein. Treatments with new ways of targeting myeloma are vital for overcoming treatment resistance in myeloma. Myeloma has genetically distinct clones, and the variation in treatment susceptibility between clones is one of the leading causes of relapse and treatment resistance in myeloma. Therefore, there is no "one-size-fits-all" treatment for myeloma, and patients need different options when other treatments aren't effective. For example, 37% of patients in the MajesTEC-1 trial did not respond to teclistamab.

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	This need for a novel target like GPRC5D is hugely important. The myeloma treatment pathway is continually evolving, patients are becoming exposed to more treatments at earlier lines, and more BCMA-targeted treatments are becoming available to patients through the NHS, clinical trials and early access programmes. New treatments with novel ways of working or targeting myeloma also give patients and their families hope and time. Hope that there will be another treatment when they relapse. It gives them more time together and also more time for a new trial or treatment to become available. Having treatment options has a significant psychological benefit to patients and their families. ***"When I was diagnosed treatment was pretty limited. My life expectancy was no more than five years. My consultant mapped out my life on an A4 sheet of paper, in a couple of lines. There was nothing on the NHS, so I went from trial to trial – and I jumped at the opportunity. At times no drugs were available, and I had to wait for the next trial or drug NICE had approved. That's when you begin to think, 'Is this it? Is there anything else available for me?. Luckily it seemed every year a new treatment was found."***
4	We are concerned that the overall survival benefit for talquetamab is being challenged unfairly and that the innovative nature of talquetamab has not been given sufficient weight. Firstly, talquetamab is part of a new, emerging class of treatments called bispecific antibodies. These bispecific antibodies work entirely differently from traditional myeloma treatments such as immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. These treatments have been a game-changer for myeloma patients, delivering unprecedented response rates and remission times in heavily pretreated patients. They are changing the patient experience at later lines, which previously saw patients have shorter remissions and higher treatment burden. Secondly, it is the only treatment for myeloma that targets myeloma cells via the GPRC5D protein. Therefore, how patients respond to and tolerate the treatment will be different from all existing treatments. We are concerned that this was not fully considered when comparing the hazard ratio for talquetamab. For example, the evidence presented by the EAG, which included Etekal et al. 2023 and Cartier et al. 2015, did not include any trials for bispecific or GPRC5D targeted treatments and therefore does not reflect the efficacy of a highly novel treatment like talquetamab. Whilst we agree that it is very rare to see an overall survival benefit with a treatment that has little demonstrated difference in progression-free survival, we also believe that talquetamab is a unique treatment—the first of its kind. The data for talquetamab comes from a controlled, clinical trial and therefore reflects its efficacy. It is possible that the difference in the hazard ratio is simply due to the innovative way talquetamab targets the myeloma cells.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Age, Gender and Overall Survival for Patients Receiving Teclistamab or Talquetamab for Multiple Myeloma

Introduction

This report was produced in partnership by the National Disease Registration Service (NDRS) and the National Institute for Health and Care Excellence (NICE). It presents patient demographic characteristics and overall survival among individuals aged 18 and over receiving either teclistamab or talquetamab for multiple myeloma. Specifically, the focus is on the subpopulation with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including:

- an immunomodulatory agent,
- a proteasome inhibitor, and
- an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

Method

A snapshot of SACT data was taken on 3rd August 2025 and made available for analysis on 20th August 2025. SACT data is only considered complete when 90% of trusts have submitted data. As a result, SACT data is considered complete up to January 2025. Patients were traced for their vital status on 5th July 2025.

Descriptive statistics of age and gender were computed, as well as overall survival (OS) Kaplan-Meier graphs and parametric fits. These are presented separately for individuals prescribed teclistamab or talquetamab.

Cohort inclusions / exclusions

A prescription for teclistamab or talquetamab was used as a proxy to identify the population of interest (n = 182), as these medicines are indicated exclusively for the target group outlined above. The following exclusions were then applied:

- teclistamab or talquetamab treatment given as part of a clinical trial (n = 3)
- gender or date of birth fields missing or implausible (n = 3)
- primary diagnosis code not including multiple myeloma ('C90'). Nulls were permitted. (n = 1)
- regimen start date outside the period 2018-04-01 to 2025-05-05 (n = 0)

The cohort was subsequently split into those receiving teclistamab (n = 139), and those receiving talquetamab (n = 39) for subsequent analysis. Note that 3 individuals received teclistamab followed by talquetamab. These individuals have been included in both populations.

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

Results - Patients who received teclistamab for multiple myeloma.

Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received teclistamab for multiple myeloma. Age is measured at the commencement of the first treatment regimen.

Table 1. Age statistics by gender for individuals initiating teclistamab

Characteristic	**Female** N = 58[1]	**Male** N = 81[1]
Age at treatment start	65, (9) : 66 (59, 73)	68, (9) : 69 (59, 75)

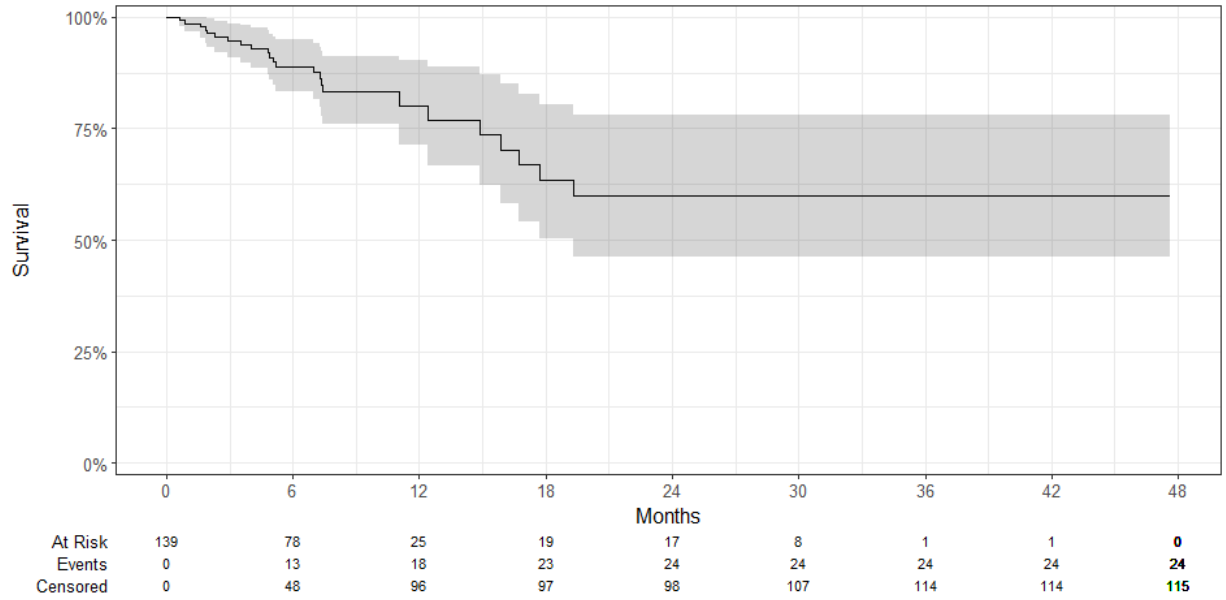
[1]Mean, (SD) : Median (Q1, Q3)

Overall Survival

Base Kaplan-Meier plot

The Kaplan-Meier plot below shows overall survival over time for those receiving teclistamab for multiple myeloma.

Figure 1: Kaplan-Meier plot of overall survival, teclistamab



Median survival was not reached. Restricted mean survival (over the whole curve) was 32.95 months. The minimum follow-up time was 0.6 months, median 6.8 months, and maximum follow-up time of 47.6 months.

Exponential

Figure 2: Kaplan-Meier plot with Exponential fit, teclistamab

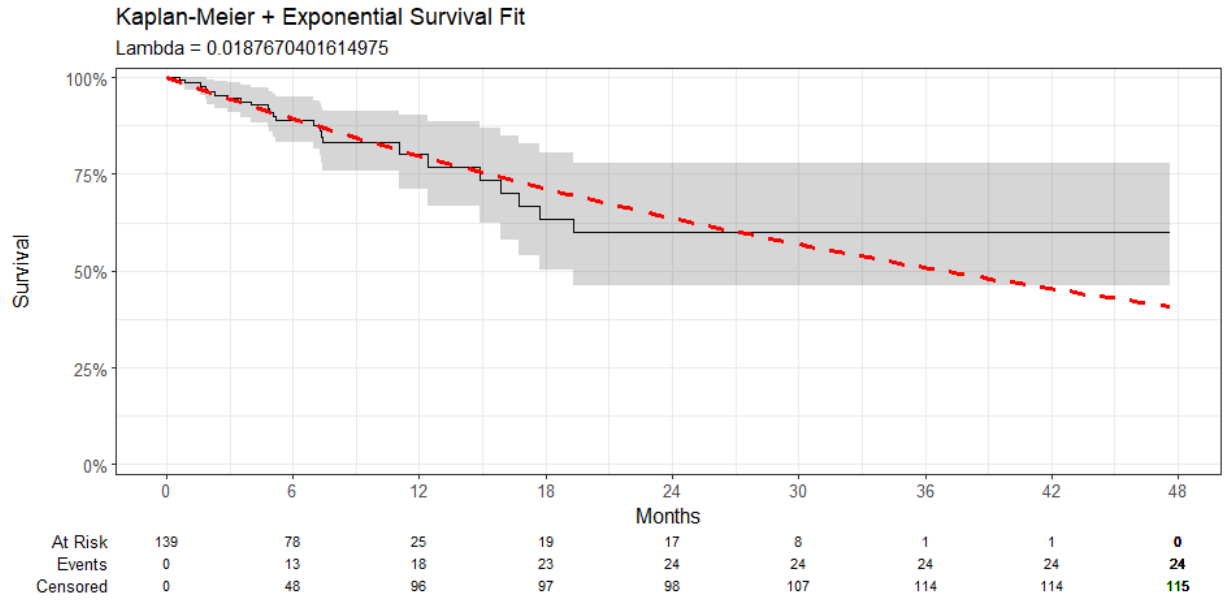


Table 2: Parameter estimates for Exponential survival model, teclistamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.976	0.204	19.47664	1.732746e-84

log-likelihood = -119.415675157288

AIC = 240.831350314576

BIC = 243.765824247707

Weibull

Figure 3: Kaplan-Meier plot with Weibull fit, teclistamab

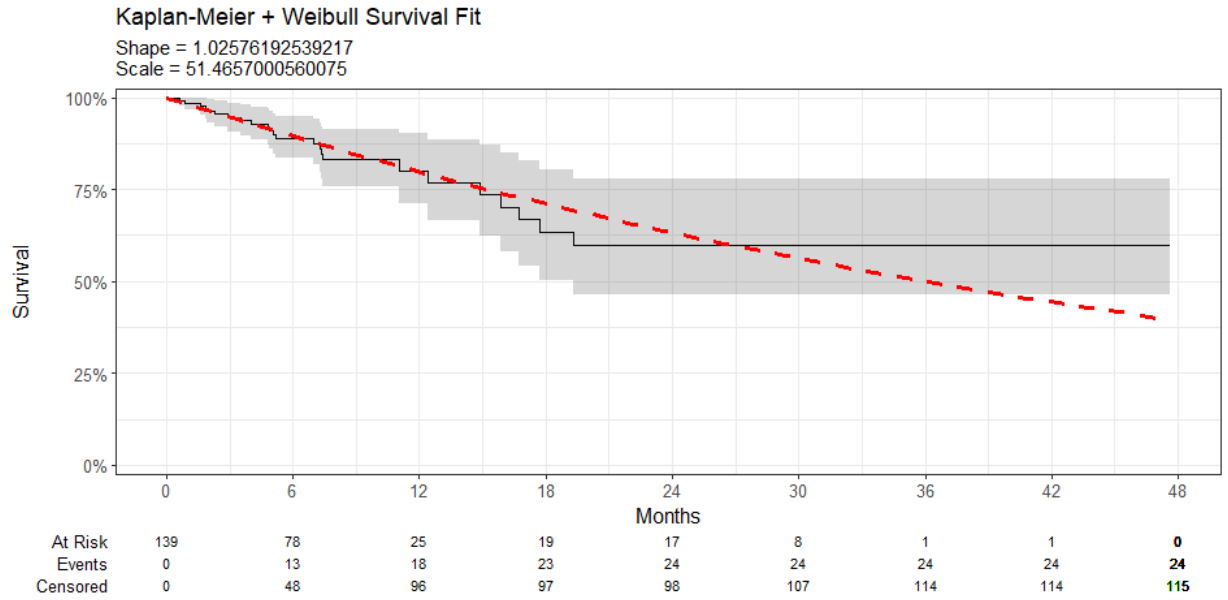


Table 3: Parameter estimates for Weibull survival model, teclistamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.941	0.288	13.6601837	1.755403e-42
Log(scale)	-0.025	0.156	-0.1631319	8.704145e-01

log-likelihood = -119.402558615164

AIC = 242.805117230327

BIC = 248.674065096588

Log-Normal

Figure 4: Kaplan-Meier plot with Log-Normal fit, teclistamab

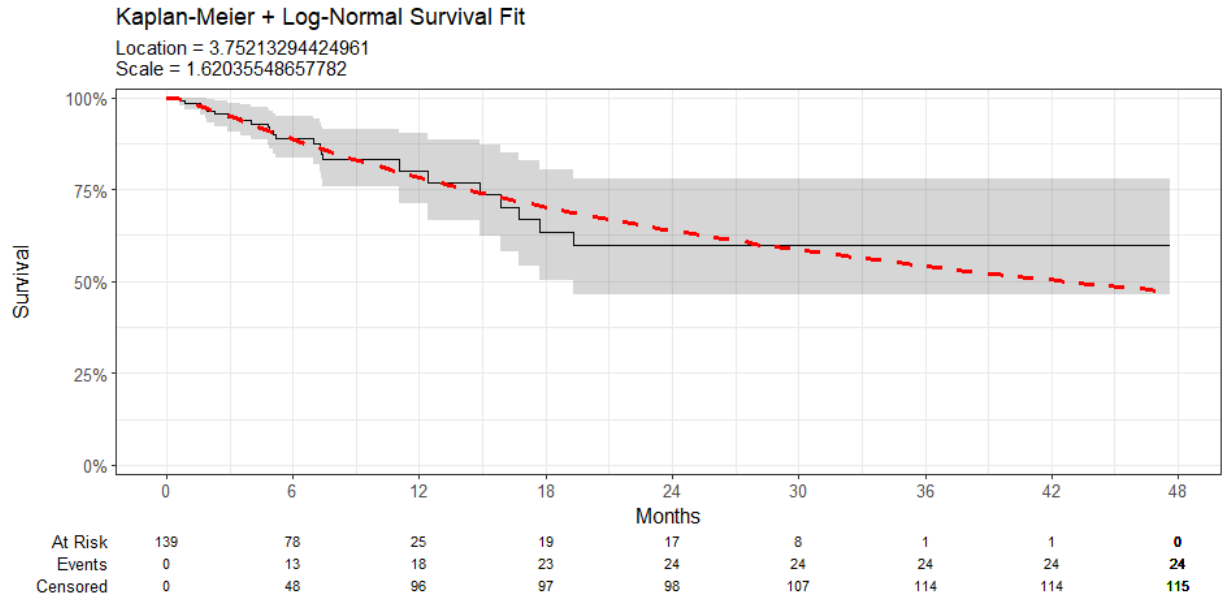


Table 4: Parameter estimates for Log-Normal survival model, teclistamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.752	0.334	11.21968	3.264518e-29
Log(scale)	0.483	0.151	3.19476	1.399472e-03

log-likelihood = -118.044660873659

AIC = 240.089321747319

BIC = 245.95826961358

Log-Logistic

Figure 5: Kaplan-Meier plot with Log-Logistic fit, teclistamab

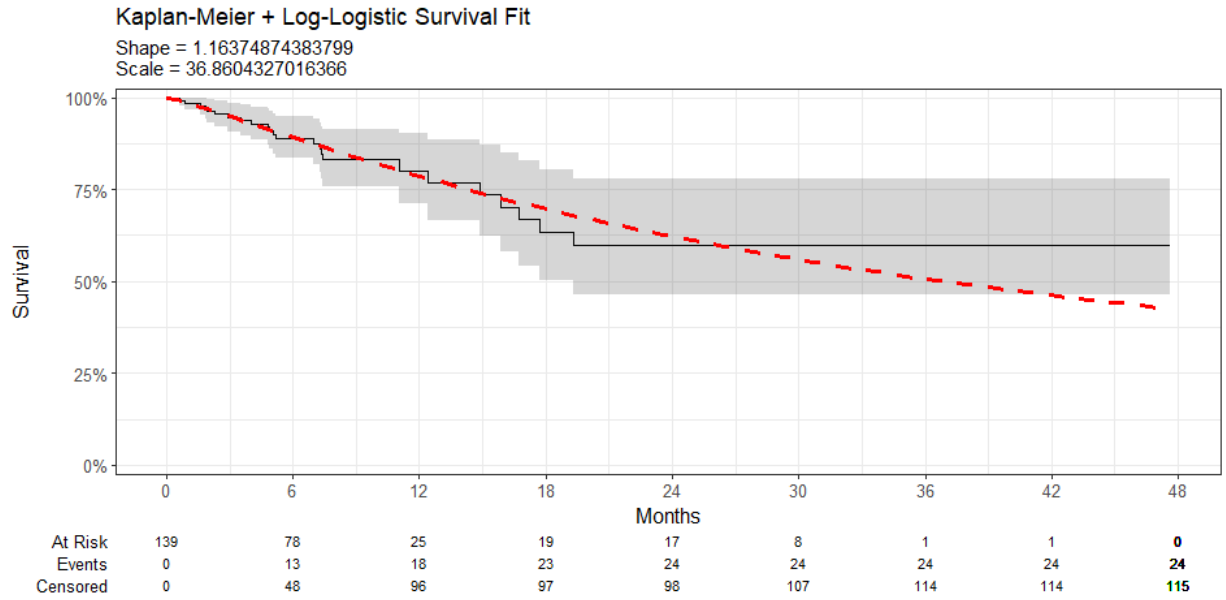


Table 5: Parameter estimates for Log-Logistic survival model, teclistamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.607	0.288	12.5177089	5.973463e-36
Log(scale)	-0.152	0.161	-0.9439076	3.452169e-01

log-likelihood = -118.704839299706

AIC = 241.409678599411

BIC = 247.278626465673

Gaussian

Figure 6: Kaplan-Meier plot with Gaussian fit, teclistamab

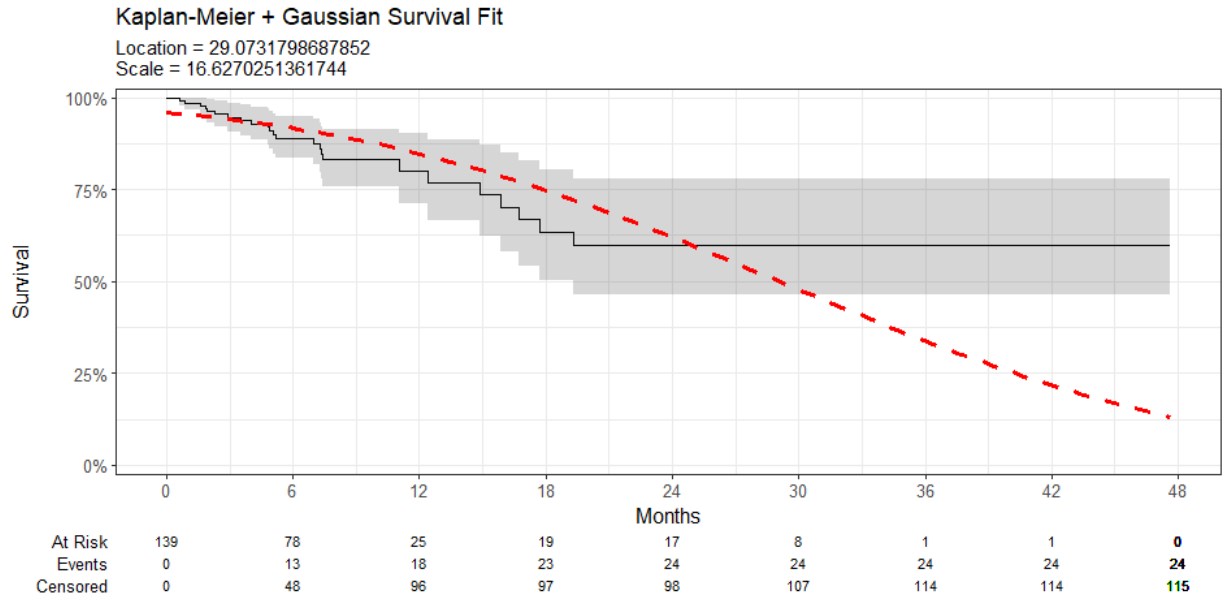


Table 6: Parameter estimates for Gaussian survival model, teclistamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	29.073	3.337	8.713111	2.956469e-18
Log(scale)	2.811	0.144	19.460796	2.360905e-84

log-likelihood = -133.859231360109

AIC = 271.718462720217

BIC = 277.587410586479

Gamma

Figure 7: Kaplan-Meier plot with Gamma fit, teclistamab

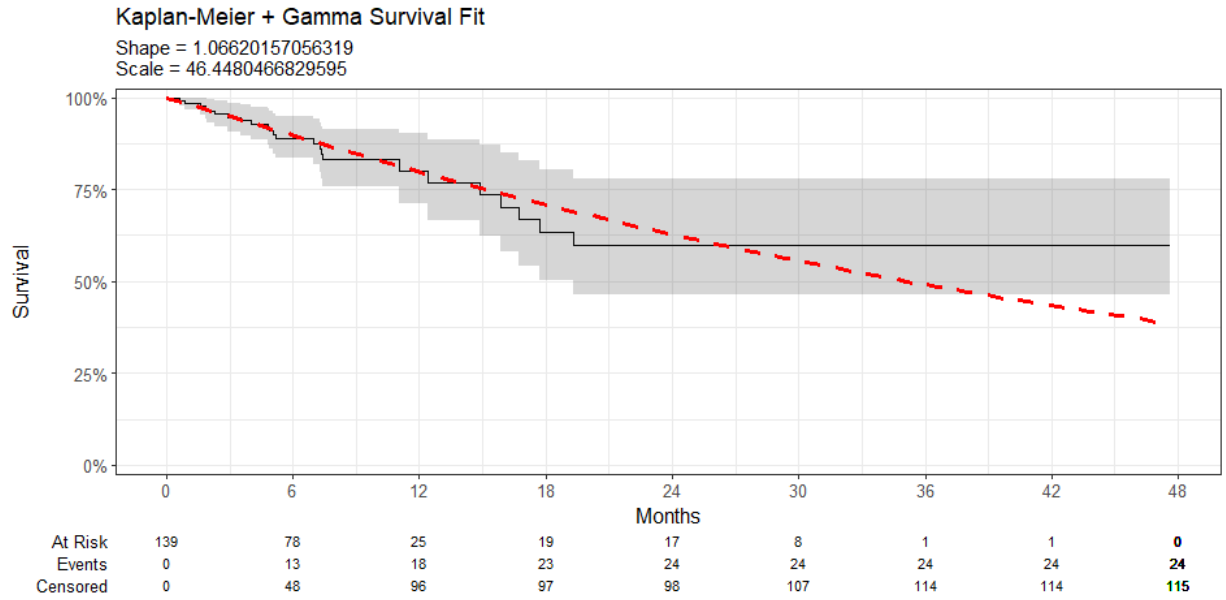


Table 7: Parameter estimates for Gamma survival model, teclistamab

Parameter	Estimate	Std. Error	L95.	U95.
shape	1.066	0.206	0.73018886	1.55683804
rate	0.022	0.010	0.00890623	0.05204406

log-likelihood = -119.361462007566

AIC = 242.722924015133

BIC = 248.591871881394

Generalised Gamma

Figure 8: Kaplan-Meier plot with Generalised-Gamma fit, teclistamab

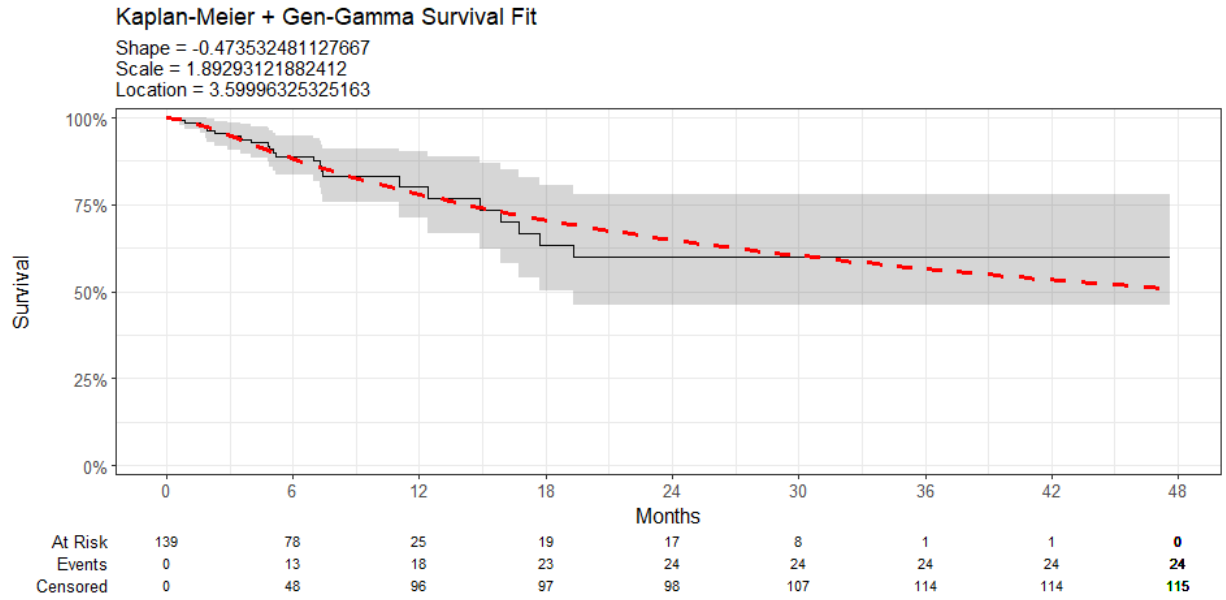


Table 8: Parameter estimates for Generalised-Gamma survival model, teclistamab

Parameter	Estimate	Std. Error	L95.	U95.
mu	3.600	0.515	2.590251	4.609676
sigma	1.893	0.591	1.026149	3.491881
Q	-0.474	1.006	-2.445845	1.498780

log-likelihood = -117.917687424186

AIC = 241.835374848372

BIC = 250.638796647764

Gompertz

Figure 9: Kaplan-Meier plot with Gompertz fit, teclistamab

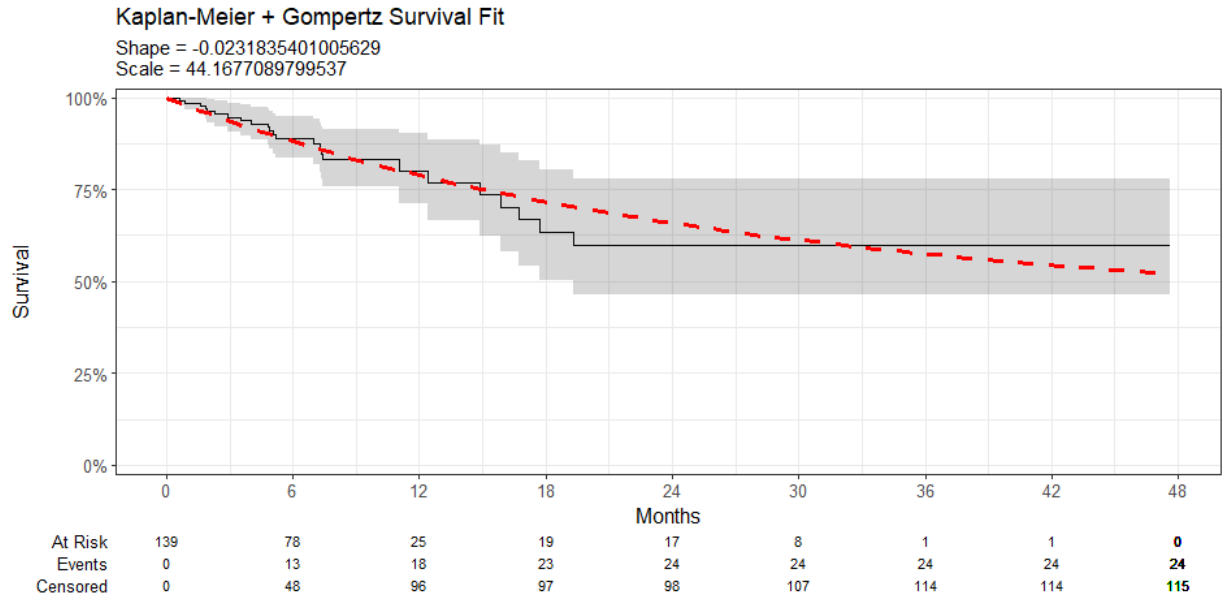


Table 9: Parameter estimates for Gompertz survival model, teclistamab

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.023	0.027	-0.07569326	0.02932618
rate	0.023	0.006	0.01298583	0.03947484

log-likelihood = -119.003089626989

AIC = 242.006179253978

BIC = 247.875127120239

Results - Patients who received talquetamab for multiple myeloma.

Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received talquetamab for multiple myeloma. Age is measured at the commencement of the first treatment regimen.

Table 10. Age statistics by gender for individuals initiating talquetamab

Characteristic	**Female** N = 16[1]	**Male** N = 23[1]
Age at treatment start	60, (11) : 61 (53, 69)	63, (7) : 64 (58, 68)

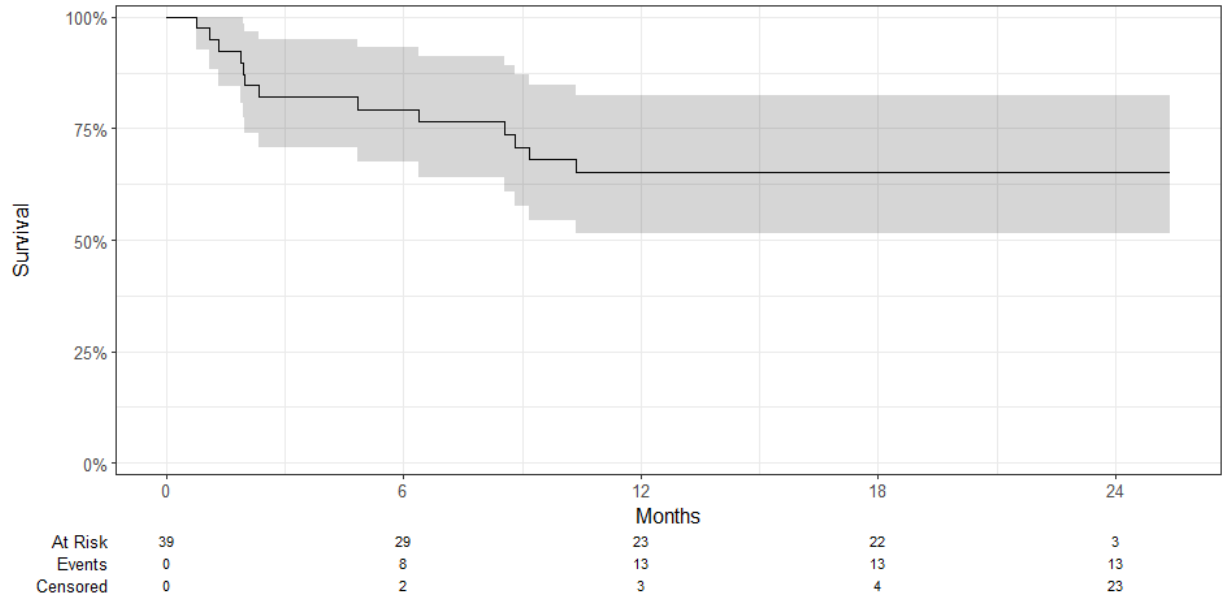
[1]Mean, (SD) : Median (Q1, Q3)

Overall Survival

Base Kaplan-Meier plot

The Kaplan-Meier plot below shows overall survival over time for those receiving talquetamab for multiple myeloma.

Figure 10: Kaplan-Meier plot of overall survival, talquetamab



Median survival was not reached. Restricted mean survival (over the whole curve) was 18.19 months. The minimum follow-up time was 0.8 months, median 21.6 months, and maximum follow-up time of 25.4 months.

Exponential

Figure 11: Kaplan-Meier plot with Exponential fit, talquetamab

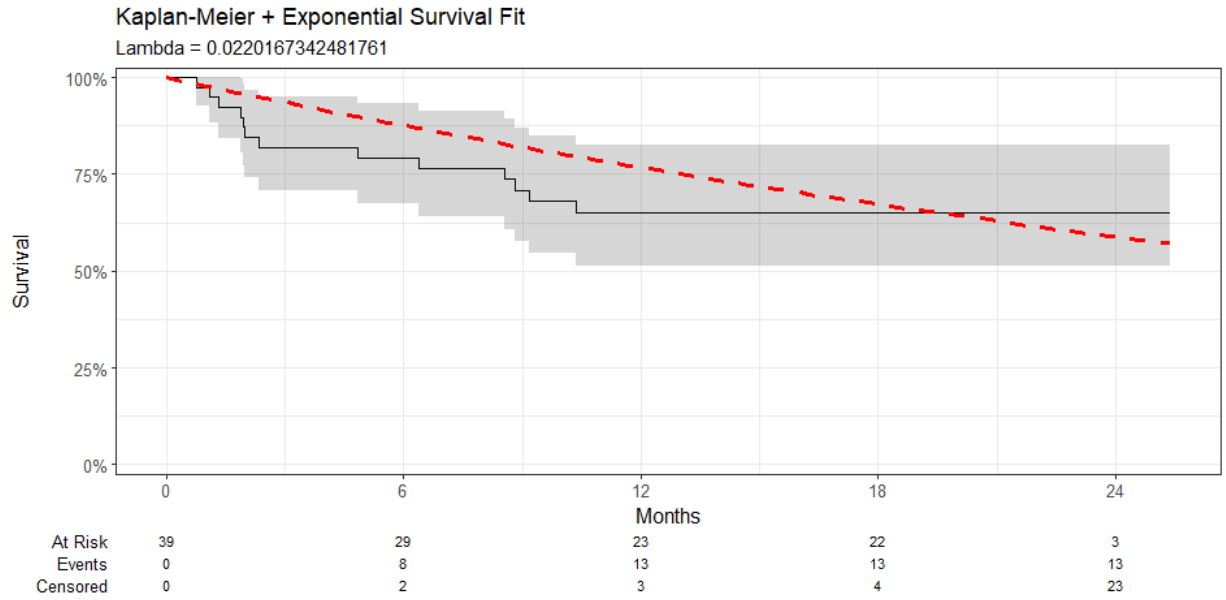


Table 11: Parameter estimates for x survival model, talquetamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.816	0.277	13.75861	4.521221e-43

log-likelihood = -62.6073820726284

AIC = 127.214764145257

BIC = 128.878325791386

Weibull

Figure 12: Kaplan-Meier plot with Weibull fit, talquetamab

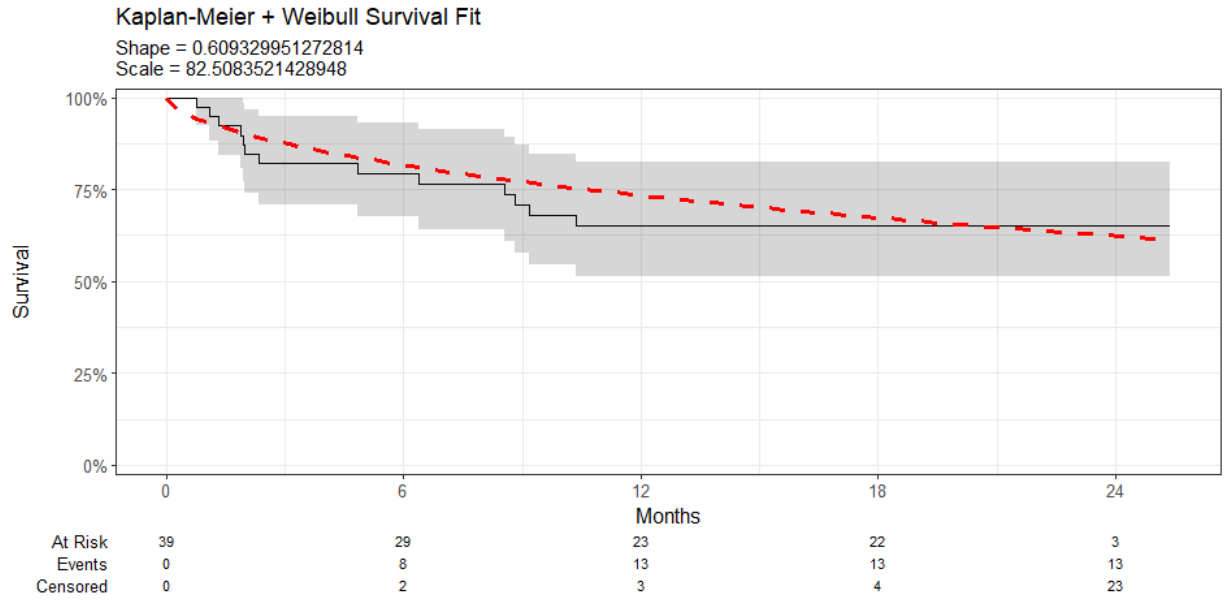


Table 12: Parameter estimates for Weibull survival model, talquetamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	4.413	0.613	7.200977	5.978252e-13
Log(scale)	0.495	0.256	1.935608	5.291569e-02

log-likelihood = -60.3306402791843

AIC = 124.661280558369

BIC = 127.988403850628

Log-Normal

Figure 13: Kaplan-Meier plot with Log-Normal fit, talquetamab

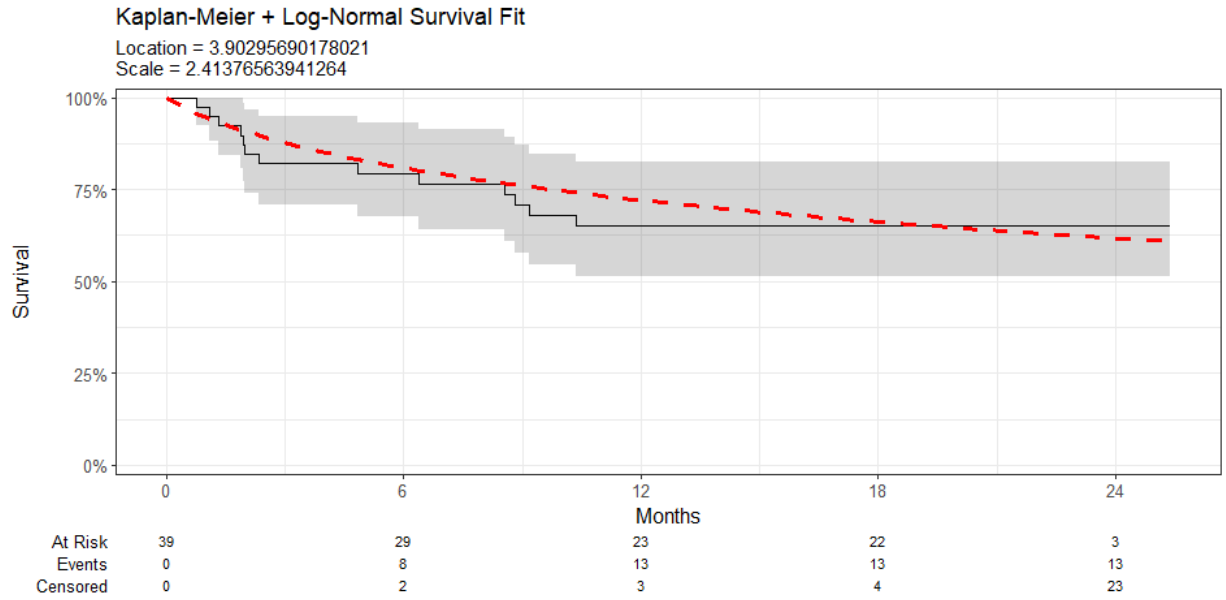


Table 13: Parameter estimates for Log-Normal survival model, talquetamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.903	0.621	6.288091	3.213945e-10
Log(scale)	0.881	0.230	3.838387	1.238452e-04

log-likelihood = -59.0180574310088

AIC = 122.036114862018

BIC = 125.363238154277

Log-Logistic

Figure 14: Kaplan-Meier plot with Log-Logistic fit, talquetamab

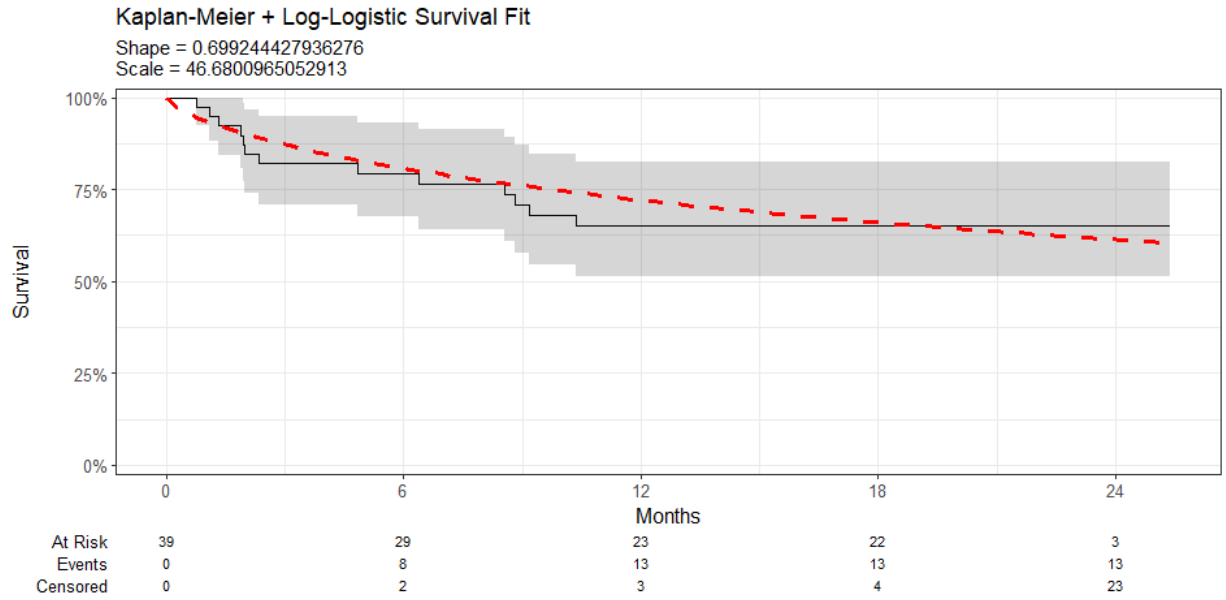


Table 14: Parameter estimates for Log-Logistic survival model, talquetamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.843	0.583	6.593140	4.306203e-11
Log(scale)	0.358	0.245	1.458768	1.446288e-01

log-likelihood = -59.8065115293291

AIC = 123.613023058658

BIC = 126.940146350918

Gaussian

Figure 15: Kaplan-Meier plot with Gaussian fit, talquetamab

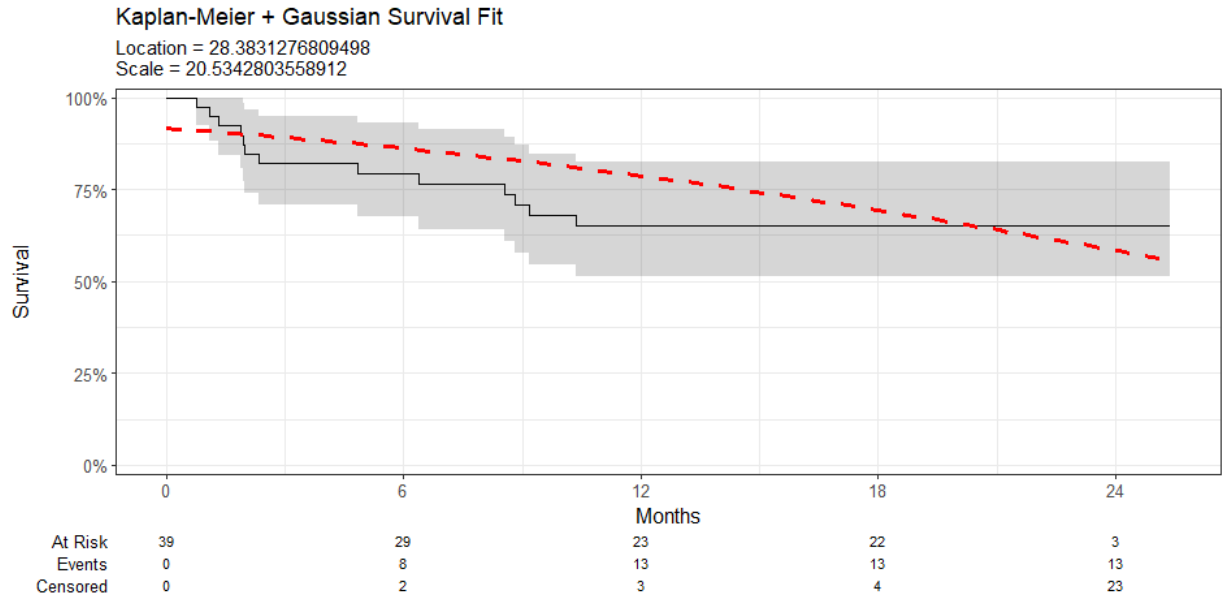


Table 15: Parameter estimates for Gaussian survival model, talquetamab

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	28.383	5.279	5.377102	7.569425e-08
Log(scale)	3.022	0.232	13.043658	6.906241e-39

log-likelihood = -71.8535378261522

AIC = 147.707075652304

BIC = 151.034198944564

Gamma

Figure 16: Kaplan-Meier plot with Gamma fit, talquetamab

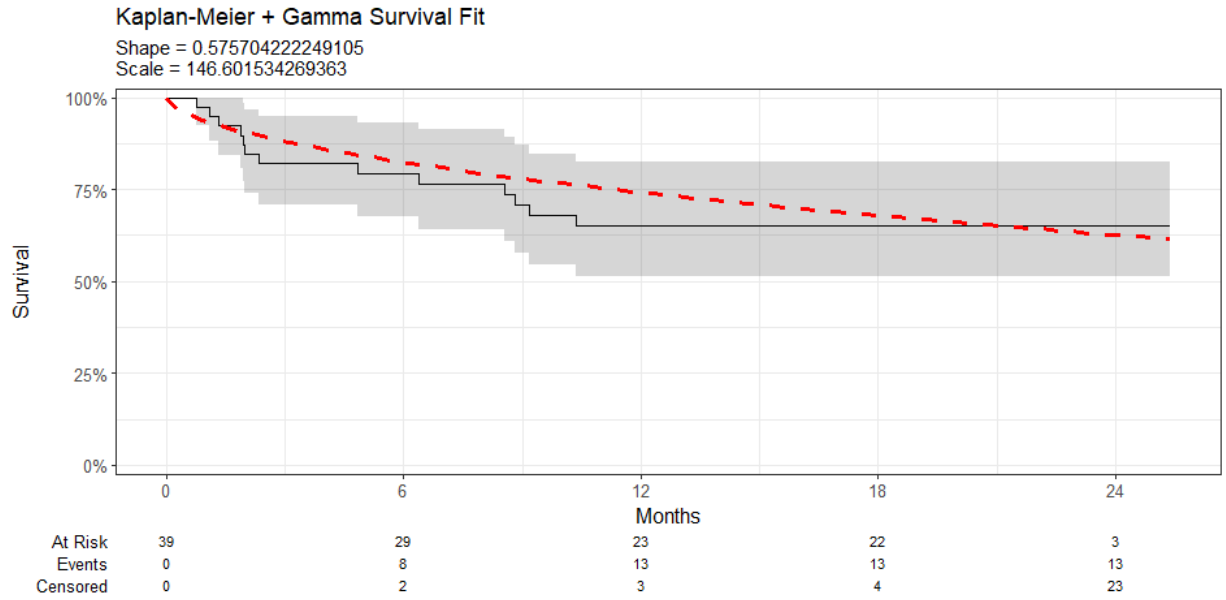


Table 16: Parameter estimates for Gamma survival model, talquetamab

Parameter	Estimate	Std. Error	L95.	U95.
shape	0.576	0.172	0.32091019	1.03279784
rate	0.007	0.006	0.00129998	0.03579204

log-likelihood = -60.6507578614962

AIC = 125.301515722992

BIC = 128.628639015252

Generalised Gamma

Figure 17: Kaplan-Meier plot with Generalised-Gamma fit, talquetamab

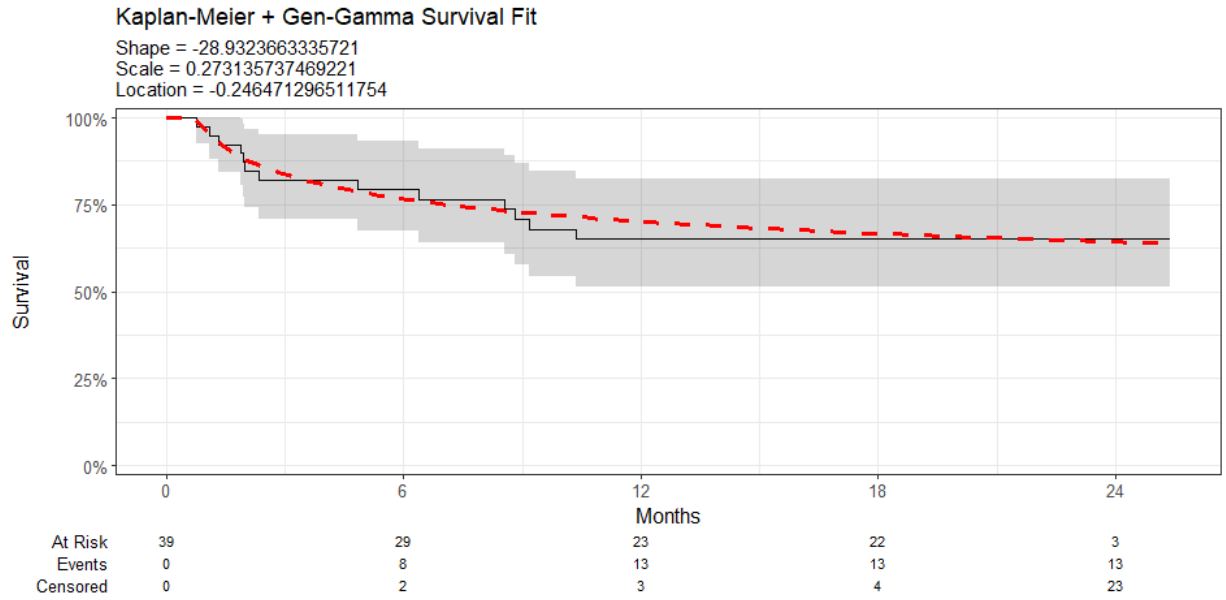


Table 17: Parameter estimates for Generalised-Gamma survival model, talquetamab

Parameter	Estimate	Std. Error	L95.	U95.
mu	-0.246	0.103	-0.44911822	-0.04382438
sigma	0.273	0.381	0.01769266	4.21661377
Q	-28.932	39.674	-106.69261780	48.82788513

log-likelihood = -55.178157179151

AIC = 116.356314358302

BIC = 121.346999296691

Gompertz

Figure 18: Kaplan-Meier plot with Gompertz fit, talquetamab

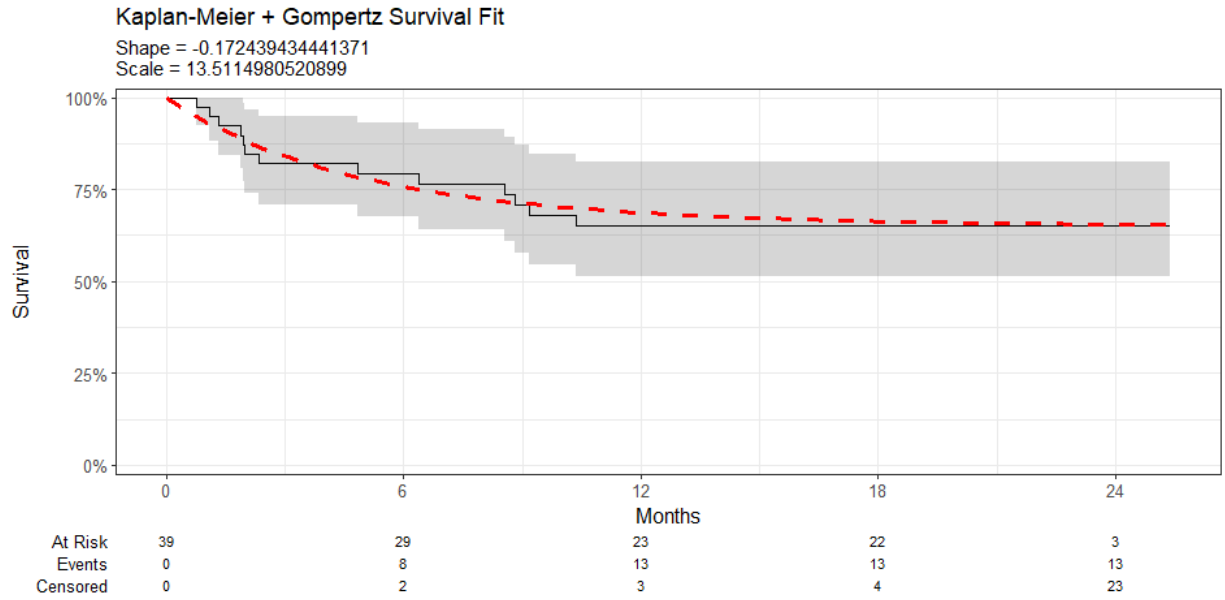


Table 18: Parameter estimates for Gompertz survival model, talquetamab

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.172	0.063	-0.29543440	-0.04944447
rate	0.074	0.030	0.03387666	0.16169344

log-likelihood = -57.0784201269155

AIC = 118.156840253831

BIC = 121.48396354609

NICE National Institute for Health and Care Excellence

Talquetamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (ID5082)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29th September 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jonhson and Johnson Innovative Medicine

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NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Esther Cheah

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
3a	**The SACT analysis is associated with an extreme degree of uncertainty consequential to the absence of adherence to the NICE RWE framework and severe limitations associated with the SACT cohorts. Fundamentally, it is quite possible that the SACT data contains a diverse and very different patient population treated with teclistamab compared to the population treated with talquetamab, and also a different patient population to that under consideration in this appraisal.** **Limitations of the SACT analysis include limited sample size and follow up, and no information on any patient baseline characteristics except age and gender. This paucity of data precludes any form of population adjustment which, in line with NICE TSD 17 and 18, would be required for a robust comparison between the talquetamab and teclistamab cohorts.[1, 2] Accordingly, the SACT analysis is associated with extensive**

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	potential for bias and unquantifiable uncertainty, and lack credibility as a valid source of evidence in this technology appraisal. On the 19th September 2025, NICE provided a report outlining a snapshot of the Systematic Anti-Cancer Therapy (SACT) data taken on 3rd August 2025 for distinct talquetamab- and teclistamab-treated cohorts.[3] While the Company supports the potential relevance and use of real-world evidence in NICE appraisals, it is imperative that such data are used responsibly and in accordance with NICE's RWE framework, be fit-for-purpose, and that the hierarchy of evidence is followed and respected. To this end, the Company strongly asserts that the limitations of the SACT analysis mean that the data provided cannot be reliably interpreted or used responsibly in this appraisal. Importantly, naïve comparisons of outcomes between the talquetamab and teclistamab cohorts and relevant trial populations (i.e., MonumenTAL-1 and MajesTEC-1), or between the talquetamab and teclistamab SACT cohorts themselves, should not be made given a number of key limitations that render the comparisons non-adherent to the scientific guidance laid out by the NICE RWE Framework. Fundamentally, it is quite possible that the SACT data contains a diverse and very different patient population treated with teclistamab compared to the population treated with talquetamab, and also a different patient population to the decision problem of this appraisal. Any such comparisons therefore would only add, rather than reduce, any uncertainty around the comparative efficacy of talquetamab and teclistamab compared to the robust trial-versus-trial ITC presented in the Company submission (CS), and it is inappropriate to model the SACT data in any scenario analyses. These issues include: **Issue 1: Lack of target trial emulation (absence of well-defined eligibility criteria)**: The talquetamab- and teclistamab-treated cohorts generated from the SACT dataset have not been designed to emulate a target trial. This means comparative efficacy conclusions cannot be reliably drawn from the data, in line with recommendations detailed in the NICE RWE Framework.[4] In particular, the absence of a well-defined eligibility criteria to define the SACT cohorts means there is a significant risk of selection bias, and represents a challenge in assessing the generalisability of cohorts. **Issue 2: Lack of baseline characteristics including uncertainty in sources of patients**: The assessment of the talquetamab- and teclistamab-treated cohorts in the SACT analysis is severely affected by the limited information on the patient baseline characteristics aside from age and gender. The limited sample size and follow-up represent additional limitations. Since teclistamab and talquetamab have been available to NHS patients through clinical trials, named patient programmes, and routine recommendation (for teclistamab only), the patient sources for each cohort may differ, leading to inherent differences in the SACT cohorts. This means that any indirect comparison of survival outcomes using the SACT cohorts is limited and creates significant

Talquetamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (ID5082)

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uncertainty for decision-making unless patient composition and prognostic factors are carefully considered.

Issue 3: Confounding bias: The absence of details on the prognostic variables in the SACT data clearly precludes any adjustment to match the two cohorts. Any measure of comparative effect would therefore have a very high likelihood of unmeasured confounding which will bias the effect measure.

Issue 4: Missing data and measurement bias: Details on missing data, or approaches taken to address missing data, are not provided for the SACT report; further details are provided in Issue 4 below. Given that missing data can cause bias and loss of precision, any comparison of the talquetamab and teclistamab SACT cohorts would lack internal validity. The absence of this detail makes it difficult to evaluate how missing data might affect the SACT data.

Issue 5: Inappropriate analysis selection: Applying restricted mean survival analyses on non-comparable follow-up durations is inappropriate for analysing overall survival data in a comparative setting.

Issue 1: The RWE talquetamab- and teclistamab-treated cohorts generated from the SACT dataset have not been designed to emulate a target trial. This is a critical requirement, recommended in the NICE RWE Framework, if comparative effectiveness assumptions were to be drawn from these data.

The NICE RWE framework clearly stipulates that RWE studies should utilise a target trial methodology which, in this case, would aim to mimic a hypothetical randomised controlled trial between talquetamab and teclistamab.[4] Accordingly, the framework recommends that the study design should be clearly defined with respect to seven key dimensions: eligibility criteria, treatment strategies, assignment procedure, follow-up period, outcomes, causal effect of interest and analysis plan. This allows for clear articulation of the study design, thereby helping to avoid selection bias.[4]

The SACT analysis includes very limited information relating to any of these dimensions. Critically, rather than application of a well-defined eligibility criteria for 4L+ TCE RRMM patients, the Company is highly concerned that "***a prescription for teclistamab or talquetamab was used as a proxy to identify the population of interest…"*** (SACT report, p1) with prior treatment classes and refractory status not defined beyond this;[3] the Company does not consider this to be a sufficiently robust approach to capturing triple-class exposed relapsed/refractory multiple myeloma patients only after 3 or more lines of treatment (4L+ TCE RRMM). This serious limitation, combined with unclear handling of missing data in deriving the talquetamab and teclistamab SACT cohorts, introduces considerable uncertainty regarding the characteristics of the patient populations included and their relevance to the decision problem.

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	Overall, the inadequate target trial emulation means the SACT dataset is subject to clear selection bias. The selection bias is particularly pronounced as teclistamab is now routinely recommended for patients in NHS clinical practice, whereas talquetamab is not. Further details on the differences between the two SACT cohorts are discussed in Issue 2. To this end, the limitations of SACT data have been acknowledged in a DSU report for the use of SACT dataset in technology appraisals – which states that "*analyses of comparative effectiveness using SACT data is prone to the limitations of observational data analyses such as selection bias and confounding, necessitating access to patient-level data in order to adjust for these*".[4] In light of this, and owing to the critical requirement for target trial emulation for any comparative effectiveness to be assessed for decision-making, the SACT data represent a fundamentally inappropriate source of comparative efficacy data, as further discussed in Issue 3. ***Issue 2: The real-world talquetamab- and teclistamab-treated cohorts in the SACT report are associated with a high degree of uncertainty due to limited sample size and/or follow-up, and lack of patient characteristics beyond age and gender. There are further uncertainties in the potential sources of patients of the two cohorts, which severely limit comparability with one another and with the indication under consideration.*** Beyond selection bias, there are severe limitations associated with both the talquetamab and teclistamab SACT data: • **Limited sample size and/or follow up:** The talquetamab SACT cohort comprises an extremely small sample size (n=39) and, without details on the patient baseline characteristics, the degree of heterogeneity between the talquetamab and teclistamab SACT cohorts cannot be assessed and would inherently influence the overall outcomes observed for the talquetamab cohort when compared to the larger teclistamab SACT data cohort of 139 patients.[3] Moreover, there is a wide range of follow-up duration within the talquetamab cohort (median [min, max]: 21.6 months [0.8, 25.4]), with the short minimum follow-up duration suggesting that the SACT data includes patients who have only just started talquetamab treatment.[3] Whilst the teclistamab SACT data has a longer maximum follow-up period, the data has a very short median follow-up of 6.8 months.[3] Indeed, there is a high degree of censoring observed in the KM curves especially in the first 12 months wherein 96 of 139 patients have been censored, resulting in highly uncertain survival outcomes.[3] • **Differences in potential sources of patients between the two cohorts:** As teclistamab is available in routine NHS practice while talquetamab is not, there is clear potential (and indeed high likelihood) for differences in the source of patients between these two cohorts.

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	The teclistamab SACT cohort is heterogenous and is likely a mix of pre-approval access (PAA) programme, routine NHS patients and potentially clinical trial patients. Given the short median follow-up and heavy censoring before 12 months, it is likely that the teclistamab SACT cohort comprises of a bolus of NHS patients as this aligns with when teclistamab was routinely made available in the NHS. Further, the Company considers **it is not possible to discount the inclusion of clinical trial patients in this cohort**. While the SACT report states that an exclusion was applied to patients who received teclistamab or talquetamab as part of a clinical trial (n=3) (SACT report, p1), the Company notes that a total of n [redacted] patients were enrolled across [redacted] clinical trials of teclistamab in the UK prior to the date of index on treatment in the SACT report (5/5/2025), and as such would anticipate the exclusion criteria to have applied to more than 3 patients as reported in the SACT report.[3] Furthermore, clinical trial patients were treated with teclistamab in the UK from [redacted] which approximately matches the maximum follow up time of 47.6 months.[3] At that time there was no other route of access to teclistamab. Feedback from SACT experts confirmed that the clinical trial field in the SACT database is unreliably captured, making it necessary to use more advanced techniques like text searches in other fields to identify trial enrolment; however, it is unclear from the SACT report if these methods were applied. As missingness is not reported or excluded in the SACT report, combined with the complete lack of inclusion criteria in the cohort definition around prior treatments, the Company considers that it is not possible to discount the inclusion of trial patients in this cohort (or in the talquetamab cohort), including those receiving teclistamab in combination with other therapies or indications other than 4L+ TCE RRMM. Of note, teclistamab is under active clinical development in earlier treatment lines, including in newly diagnosed multiple myeloma. This creates a high level of uncertainty and likelihood of inclusion bias with respect to the survival outcomes reported for the teclistamab SACT cohort. The talquetamab SACT cohort likely comprises PAA patients (and potentially trial patients) given it is not yet available for NHS patients. **PAA patients and routine NHS patients represent two fundamentally different cohorts of patients**. PAA patients represent those who have exhausted all approved commercially available and clinically appropriate lines of treatment and are ineligible for a trial. PAA patients generally have a worse prognosis and face shorter life expectancy, leading to poorer overall survival in cohorts with more PAA patients due to selection bias, rather than differences in clinical effectiveness. In this context, it is not unreasonable to consider that the SACT dataset may include early treatment-line teclistamab patients and later-line talquetamab patients who have exhausted other accessible treatment options and are therefore more unwell. Without adjusting the baseline characteristics and establishing clearly defined inclusion/exclusion criteria, potential discrepancies in patient populations precludes any meaningful comparative assessments of teclistamab versus talquetamab using SACT data, or appropriate

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	comparison between the SACT cohorts and to their respective registration trial populations. Consequently, this limitation seriously negates the relevance of the SACT data for the decision problem under consideration in this appraisal. ***Issue 3: No information is available for any key prognostic patient baseline characteristics in the talquetamab and teclistamab SACT cohorts, meaning that they cannot be formally adjusted in an ITC in line with NICE TSD 17 and 18.[1, 2]*** As detailed under Issue 1, the real-world talquetamab and teclistamab cohorts generated from the SACT dataset have not been designed to emulate a target trial. The absence of well-defined eligibility criteria introduces selection bias into the cohorts, posing a considerable challenge in assessing the degree of overlap between the two patient cohorts and therefore determining whether the principles of generalisability have been satisfied.[4] Careful evaluation of patient characteristics, and particularly those of prognostic significance, is therefore essential to ensure a rigorous comparison. However, there is no available information regarding baseline characteristics in the SACT data analysis other than age and gender. As outlined in Section 2.10.3 of the CS, clinicians identified several key prognostic variables for multiple myeloma - refractory status, cytogenetic profile, ISS stage, time to progression on last regimen and extramedullary plasmacytoma. Since none of these variables are reported in the SACT report, adjustment for covariates is impossible, leaving considerable imbalances and potential confounding bias between the two patient cohorts. This creates significant and unquantifiable uncertainty around the comparability of the effectiveness data reported for talquetamab and teclistamab in the SACT report; any comparison would be heavily confounded and simply uninterpretable without understanding the direction of bias. By contrast, the Company has presented the Committee with a rigorous ITC comparing 2 registrational trials, adjusting for all 17 prognostic covariates using individual patient data (standardised mean differences (SMD) of less than 0.2 across all factors). Therefore, it is unclear how the SACT data would reduce clinical uncertainty as the implied comparative effectiveness from the SACT analysis lacks validity. ***Issue 4: The SACT report lacks details on missing data, and any approaches taken to address missing data. It is therefore not possible to assess the impact of bias due to missing data on the SACT dataset.*** The Company is concerned that no details on missing data or approaches taken to address missing data have been outlined in the SACT report. NICE's RWE framework states that limitations in data quality related to *"missing data, measurement error or misclassification can cause bias and loss of precision"*.[4] For example, the definition of MM within the cohort relies on an ICD-10 M90 code, for which missingness has been permitted (SACT report, p1).[3] Permitting missingness cannot fully exclude the potential for off-label use of talquetamab and

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	teclistamab in the data set. As noted in Issue 2, missingness of the clinical trial field has also not been reported or excluded, introducing potential for inclusion of treated patients not representative of the intended indication and creating potential for inclusion bias in the OS measurement. Given the limited sample size of the SACT dataset and follow-up period as well as the lack of patient demographic baseline characteristics or subsequent treatment data, it becomes even more critical that details on missing data are reported, and clear methods to mitigate such missing data are undertaken. With no such methods outlined or undertaken to address missing data captured in the report, the SACT data lack internal validity. Furthermore, it is not possible to assess the impact of bias due to missing data on any comparative efficacy estimates drawn from the data. ***Issue 5: Using restricted mean survival analyses, based on non-comparable follow-up durations, is an inappropriate means for analysing overall survival data.*** The SACT analyses report a restricted mean survival duration (over the whole curve) for the talquetamab and teclistamab cohorts. However, it should be noted that the restricted mean survival duration is dependent on the maximum follow-up time, which is not comparable between the two cohorts (25.4 months and 47.6 months for talquetamab and teclistamab, respectively).[3] Therefore, any naïve comparisons of restricted mean survival duration as a means to compare survival between the cohorts is wholly inappropriate and misleading. ***In summary, owing to the high degree of uncertainty associated with the SACT report, the results of the analysis lack credibility and should not be used for decision-making in this appraisal. Inappropriate consideration of the data would prejudice the appraisal, accordingly.*** For the reasons outlined above, the SACT analyses do not adhere to the NICE's RWE framework and are associated with an extremely high degree of uncertainty, to the point where these data are uninterpretable and should not be used in this NICE appraisal. The results presented in the SACT are subject to considerable bias, thereby introducing high uncertainty to the appraisal: • Any conclusions drawn from a naïve comparison of the talquetamab- and teclistamab-treated cohorts in the SACT report are invalid and therefore do not resolve any uncertainty regarding the comparative effectiveness of talquetamab compared to standard of care. Consequently, such comparison should not be incorporated into any modelling scenarios or be used to inform extrapolation choice in the current economic model as they are uninformative. As such, any due consideration of the data is inappropriate and may prejudice the appraisal.

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	• The absence of detailed patient baseline characteristics in the SACT cohorts introduces significant uncertainty when potentially comparing the SACT cohorts with trial patient populations, unless differences between the two patient populations are adequately controlled for In comparison to the SACT data and its aforementioned uncertainties, the Company emphasises that MonumenTAL-1 and MajesTEC-1 are both registrational trials, based on which the respective marketing authorisations for talquetamab and teclistamab have been granted. The ITC analyses conducted by the Company adjust for all 17 prognostic factors in line with NICE TSD 17, including both priority and non-priority factors, and therefore represents a considerably more rigorous and less uncertain analysis than any comparative analysis using the SACT cohort data [1]. As outlined by the NICE methods for health technology evaluations (PMG36), a clear preference for non-randomised studies is stated in the absence of RCT evidence, to form the primary source of evidence.[5] As per the NICE RWE framework, real-world data are meant to fill evidence gaps and RWE studies are required to use "fit-for-purpose" data. Due to the substantial limitations identified in the SACT analysis, J&J does not view this information as fit-for-purpose data or a responsible use of real-world data. As a result, the report should be excluded from consideration as evidence and deemed irrelevant for decision-making purposes.[4]
3b	**ITC of REALiTEC and REALiTAL** As stated on pages 2 and 3, while the Company acknowledges the potential relevance and use of real-world evidence in NICE appraisals, provided that such data are used responsibly, adhere to NICE's RWE framework, are fit-for-purpose, and follow the established hierarchy of evidence. As such, the Company strongly maintains that an indirect treatment comparison informed by the MajesTEC-1 and MonumenTAL-1 clinical trials remains the most robust source of evidence to inform decision making. However, the Company also recognises that the Committee may seek supplementary real-world evidence on how teclistamab and talquetamab may perform in clinical practice, where such comparisons are conducted according to NICE's framework.[4] At the time of writing, the Company has received confirmation from NICE that the SACT report cannot be updated to address the aforementioned limitations. To support decision-making in the upcoming Appraisal Committee Meeting, the Company has conducted an indirect treatment comparison of the emerging REALiTEC and REALiTAL studies, which are retrospective, non-interventional studies designed to evaluate the real-world outcomes of teclistamab and talquetamab, respectively, in patients with TCE RRMM treated outside of clinical trials.[6, 7] These studies aim to provide early insights into the safety, effectiveness, and

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	treatment patterns of these therapies in the real-world setting, including the UK. The significant advantage these two studies offer over the SACT data provided is that, as per the protocols for both studies which align with the target trial approach of the NICE's RWE framework, clearly defined inclusion / exclusion criteria were applied and extensive baseline information for the REALiTEC and REALiTAL populations were collected in addition to the outcomes of interest. This enables a more robust indirect treatment comparison than with SACT data, as key prognostic factor imbalances between populations can be adjusted, which significantly reduces confounding bias. The study design and objectives are presented in Appendix 1. **Baseline Characteristics of the Study Populations** The full baseline characteristics of the REALiTEC and REALiTAL studies presented in Table 2 Appendix 2 reflect the advanced disease and heavily pretreated nature of the patient populations. In the REALiTEC study, the median age was 66 years (range: [redacted]), with [redacted] male patients and [redacted] of those with available data having an ECOG performance status of 1 or higher. Moreover, 78.8% of patients were triple-class refractory and 44.2% were penta-class refractory.[7] Additionally, [redacted] of patients had prior exposure to BCMA-targeted therapies. Regarding lactate dehydrogenase (LDH) levels, [redacted] of patients had LDH <280 U/L, while [redacted] had LDH ≥280 U/L. In the REALiTAL study, the median age was 65 years (range: [redacted]), with [redacted] male patients and [redacted] of those with available data having an ECOG performance status of 1 or higher. Similarly, 69.9% of patients were triple-class refractory, and 39.8% were penta-refractory.[6] Prior exposure to BCMA-targeted therapies was higher in this cohort, at [redacted]. For LDH levels, [redacted] of patients had LDH <280 U/L, while [redacted] had LDH ≥280 U/L. These data highlight the breadth of data collected in both studies along with the heavily pretreated nature of both populations, with differences in BCMA exposure, high risk disease status, LDH levels, and refractoriness that are critical for indirect treatment comparisons. **ITC methods** An ITC was conducted between talquetamab and teclistamab using patient level data from REALiTEC and RealiTAL using multivariable regression to control for differences in baseline characteristics between the two study populations. This approach allows for a more robust comparison of outcomes by accounting for observable prognostic variables that may influence treatment effects, an approach that was not possible with the SACT data given the lack of patient characteristics. A multivariable regression approach was used in favour of alternative approaches such as inverse probability of treatment weighted (IPTW) which may be less reliable where there are small sample sizes due to underestimated variance in the effect

estimates. In such cases, regression approaches are recommended (Raad 2020, Chesnaye 2021).[8, 9]

Multivariable regression is a statistical technique that models the relationship between a dependent variable (e.g., overall survival,) and multiple independent variables (e.g., baseline characteristics). In an ITC, this method is used to estimate the treatment effect of one therapy relative to another while controlling for confounding factors that could bias the comparison. By including relevant baseline characteristics as covariates in the regression model, the analysis controls for differences in patient populations, thereby isolating the effect of the treatment itself. The observable variables that were available for adjustment are presented in Table 2 of Appendix 2 and include a wide range of clinically relevant prognostic factors, typically reported in clinical studies in multiple myeloma.

By including these variables in the regression model, the analysis adjusts for differences in the distribution of these factors between the REALiTEC and REALiTAL cohorts. This adjustment ensures that the estimated treatment effect reflects differences attributable to the therapies themselves, rather than differences in patient or disease characteristics.

Consistent with the approach used for the main ITC in the Company Submission, the results incorporate a two-stage adjustment to account for patients who received therapies not available in UK clinical practice. This was implemented by fitting an accelerated failure time (AFT) model with an Exponential distribution to estimate an acceleration factor, which was then applied to 'shrink' the survival times of patients receiving non-routine subsequent treatments. Full details of this methodology are provided in the Company Submission and the Company's response to clarification questions. Appendix 3 presents the breakdown of subsequent treatments pre- and post-two stage adjustment.

ITC Results

Table 1 presents the results from the multivariable regression alongside the naïve observed hazard ratios (HR). These results indicate an observed HR of [redacted] without multivariable regression nor adjustment for subsequent therapies. Accounting for subsequent therapies not available in UK clinical practice results in an observed HR of [redacted] without multivariable regression. The multivariable regression which controls for all available prognostic factors as well as non-UK subsequent therapies results in a HR of [redacted]. Additional outputs in Figure 1 of Appendix 2 further underscore the importance of access to—and adjustment for—baseline characteristics.

These findings demonstrate that adjusting for observable differences between the REALiTEC and REALiTAL cohorts via multivariable regression improves the relative outcomes for talquetamab compared with teclistamab. This improvement reflects the bias introduced by population imbalances in the naïve comparison, which favoured teclistamab, and highlights the

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critical need for formal adjustment in ITCs to ensure robust and credible comparisons (as emphasised in Issue 3). After adjustment, the point estimate HR is [redacted], [redacted], indicating a [redacted] reduction in the risk of death with talquetamab versus teclistamab in real-world practice—consistent with the conclusions of the MonumenTAL-1 versus MajesTEC-1 ITC submitted in the Company Submission.

Table 1: Summary of REALiTEC vs REALiTAL ITC results

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

Abbreviations: HR: hazard ratio; ITC: indirect treatment comparison.

Summary

The Company supports the value of RWE in NICE appraisals but emphasises that such data must be fit-for-purpose and align with NICE's RWE framework and respect the long-standing hierarchy of evidence. While RWE may potentially fill evidence gaps and supplement trial evidence, the pivotal MajesTEC-1 and MonumenTAL-1 clinical trials remain the most robust sources of clinical evidence and thus are most informative for decision making.

As the SACT analysis cannot be reliably interpreted nor is fit-for-purpose as a real-world evidence in the context of this appraisal decision, an additional ITC was conducted using data from the recent REALiTEC and REALiTAL studies, which were designed with clearly defined inclusion criteria and extensive baseline data collection. This approach allowed for a more robust comparison than the SACT data by controlling for key prognostic imbalances across both populations. It is important to note that these studies were not powered nor designed with the intent to use for ITCs, which limits the ability of the analysis to achieve statistical significance. Despite this, adjusted results from the ITC of REALiTAL and REALiTEC demonstrate that talquetamab is associated with a [redacted] reduction in the risk of death compared to teclistamab ([redacted]) in real-world clinical practice.

This analysis demonstrates that population imbalances can introduce substantial bias into ITCs, underscoring the critical need to adjust for baseline differences to ensure credible and

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	robust comparisons of clinical effectiveness. By controlling for these imbalances, the analysis strengthens confidence in the comparative findings and may also provide supplementary real-world evidence to inform decision-making. While this ITC may be considered less robust than the MajesTEC-1 versus MonumenTAL-1 ITC, it can play an important role in contextualising the updated Company Base Case. This Base Case is based on the most rigorous ITC available—comparing MajesTEC-1 and MonumenTAL-1, adjusted for the impact of COVID—which yields a hazard ratio of [redacted], offering the most robust estimate of the relative treatment benefit of talquetamab over teclistamab.
3c	**Broader implications of use of pre-approval access program data in NICE appraisals** As described in 3a, the inappropriate use of real-world evidence introduces additional uncertainty into the decision-making process. This has the potential to complicate the appraisal and could delay access to talquetamab for patients. Pre-approval access (PAA) programmes, often referred to as compassionate use programs, allow patients with significant unmet needs including those who are not eligible for clinical trials and have exhausted all commercially available options, to access medicines earlier and prior to reimbursement. However, these patients form a population that may not be fully representative of those expected to be treated in routine clinical practice. Since PAA patients are included in the real-world SACT dataset, outcomes from these cohorts are captured in any SACT analyses and may easily differ from those observed in clinical trials or anticipated in future clinical practice, potentially resulting in conflicting evidence and increased uncertainty during appraisal. This undesirable scenario could have wider ramifications extending far beyond this particular appraisal, potentially establishing a precedent whereby pre-reimbursement programmes impede the appraisal process for routine access to medicines within the NHS and, consequently, substantially reduce the appeal of the UK healthcare for early access initiatives.

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Appendix 1. Study design and objectives of REALiTAL and REALiTEC

Study Design and Objectives

Both studies are retrospective, non-interventional in scope, relying on data from patient medical records. Patients aged 18 years or older with RRMM who received at least one dose of teclistamab (REALiTEC cohort) or talquetamab (REALiTAL cohort) outside of clinical trials were eligible for inclusion.[6, 7] The REALiTEC study included patients who initiated teclistamab treatment on or before [redacted] (median duration of follow up of [redacted] months (range, [redacted] months), while the REALiTAL study included patients who initiated talquetamab treatment on or before [redacted] (median duration of follow up of [redacted] months (range, [redacted] months). Data collection encompassed baseline characteristics, treatment details, safety outcomes, and effectiveness measures. The REALiTEC cohort enrolled 113 patients of which [redacted] were from the UK, while the REALiTAL cohort included 93 patients of which [redacted] were from the UK. Patients were enrolled from both pre-approval access and commercial programmes, importantly however, given the availability of baseline characteristics for both studies, any imbalances across populations can be appropriately controlled for to ensure comparability.

The primary objectives of these studies were to describe patient and disease characteristics, treatment patterns, and the safety and effectiveness of teclistamab and talquetamab in real-world settings.

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Appendix 2. Supplementary REALiTEC vs REALiTAL ITC results

Table 2: Summary baseline characteristics and demographics of REALiTEC and REALiTAL

Characteristic	REALiTEC (n=113)	REALiTAL (n=93)
BCMA status		
BCMA naive	[redacted]	[redacted]
BCMA exposed	[redacted]	[redacted]
Refractory status		
<= Double refractory	[redacted]	[redacted]
Triple refractory	39 (34.5%)	28 (30.1%)
Penta refractory	50 (44.2%)	37 (39.8%)
ISS		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
Missing	[redacted]	[redacted]
EMD		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
n prior lines <=4 vs 4+		
<=4	[redacted]	[redacted]
>4	[redacted]	[redacted]
Years since diagnosis		
<6 years	[redacted]	[redacted]
>= 6 years	[redacted]	[redacted]
Avg duration of prior lines (months)		
<10	[redacted]	[redacted]
10 to 14	[redacted]	[redacted]
>=15	[redacted]	[redacted]
Age		
<65	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Haemoglobin		
<120	[redacted]	[redacted]
>=120	[redacted]	[redacted]
Missing	[redacted]	[redacted]

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LDH		
<280	[redacted]	[redacted]
>= 280	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Creatinine Clearance		
<60	[redacted]	[redacted]
60-<90	[redacted]	[redacted]
>=90	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG		
ECOG 0	[redacted]	[redacted]
ECOG 1+	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Gender		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Prior transplant		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Other/Not reported	[redacted]	[redacted]
Cytogenetic risk		
Standard Risk	[redacted]	[redacted]
High risk	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: BCMA: B-cell maturation antigen; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary plasmacytoma; ISS: International Staging System; LDH: lactate dehydrogenase.

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Talquetamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (ID5082)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29th September 2025. Please submit via NICE Docs.

Figure 1: REALiTEC vs REALiTAL OS incremental adjustment in the multivariate model (and post subsequent treatment adjustment)

Abbreviations: BCMA: B-cell maturation antigen; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary; HR: hazard ratio; ISS: International Staging System; LDH: lactate dehydrogenase; OS: overall survival; TAL: talquetamab; TEC: teclistamab.

Appendix 3. REAiTAL and REALiTEC subsequent treatments before and after two-stage adjustment

Table 3: Overview of REALiTAL and REALiTEC subsequent treatments before and after two-stage adjustment

Patients receiving subsequent therapy (%)	REALiTAL [redacted[a]]	Patients receiving subsequent therapy (%)	REAliTEC [redacted[a]]
Before adjustment			
Investigational agent[b]	[redacted]	Bendamustine-based regimens	[redacted]

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Autologous stem cell	[redacted]	Bortezomib-based	[redacted]
Belantamab mafodotin	[redacted]	Carfilzomib-based	[redacted]
Bendamustine-based	[redacted]	CAR-T	[redacted]
Bortezomib-based	[redacted]	Ciltacabtagene autoleucel	[redacted]
Talquetamab + teclistamab (combination)	[redacted]	Cyclophosphamide-based regimens	[redacted]
Daratumumab-based	[redacted]	Daratumumab-based	[redacted]
Pomalidomide-based	[redacted]	Dexamethasone monotherapy	[redacted]
Panobinostat	[redacted]	Doxorubicin	[redacted]
Carfilzomib-based	[redacted]	Elotuzumab-based	[redacted]
Isatuximab-based	[redacted]	Forimtamig	[redacted]
Ciltacabtagene autoleucel	[redacted]	Isatuximab-based	[redacted]
Cyclophosphamide-based regimens	[redacted]	Lenalidomide-based	[redacted]
Dexamethasone monotherapy	[redacted]	Melphalan-based regimens	[redacted]
Elotuzumab-based	[redacted]	Mezigdomide + tazemetostat+ dexamethasone	[redacted]
Ixazomib-based	[redacted]	Modakfusp Alfa	[redacted]
Elranatamab	[redacted]	Panobinostat-based	[redacted]
Idecabtagene viclucel	[redacted]	Pomalidomide-based regimens	[redacted]
Linvoseltamab	[redacted]	Selinexor	[redacted]
Melphalan-based	[redacted]	Talquetamab	[redacted]
Mezigdomide	[redacted]	Teclistamab	[redacted]
Obinutuzmab	[redacted]	Teclistamab-lenalidomide	[redacted]
Selinexor-based	[redacted]	Thalidomide-based	[redacted]
Teclistamab	[redacted]		
Thalidomide based	[redacted]		
Venetoclax	[redacted]		
Following adjustment of non-UK treatments[c]			
	REALiTAL		**REALiTEC**
Bendamustine	[redacted]	Bendamustine	[redacted]

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Bortezomib-based	[redacted]	Bortezomib-based	[redacted]
Cyclophosphamide-based	[redacted]	Cyclophosphamide-based	[redacted]
Dexamethasone	[redacted]	Dexamethasone	[redacted]
PomDex	[redacted]	Dexamethasone+thalidomide	[redacted]
Melphalan	[redacted]	Lenalidomide	[redacted]
Panobinostat	[redacted]	Pomalidomide	[redacted]
Selinexor	[redacted]	Melphalan	[redacted]
Teclistamab	[redacted]	Panobinostat	[redacted]
Thalidomide-based	[redacted]	Selinexor	[redacted]
		Talquetamab	[redacted]

Footnotes:
[a] Total N refers to patients who survived progression who started at least one subsequent on or after progression date
[b] Investigational agents include ABBV 453
[c] Percentages were derived following removal of non-UK subsequent treatments with patients re-weighted such that the total percentage of patients summed to 100%
Abbreviations: UK: United Kingdom.
Source: J&J IM. Data on File.

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External Assessment Group response to draft guidance comments form

Title: *ID5082 Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies*

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue.

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Introduction

In their response to Draft Guidance Document (DGD), the company has

(1) Revised the Company base case to incorporate the Committee's preferred assumptions, presented in Appendix A of company DGD response.
(2) Provided additional analyses as part of this response, including those requested by the Committee and additional commentary.

In this document, the EAG provide a point-by-point response to the company DGD submission, where appropriate.

Comment 1: Indirect treatment comparison (ITC) analyses using pooled, unweighted data for Cohort A+C in MonumenTAL-1

The committee requested pooled unweighted data for Cohort A (once weekly) and C (every two weeks) in MonumenTAL-1. The company provided this analysis in Comment 1 of their response.

For ease, the EAG have replicated indirect treatment comparison (ITC) analyses using pooled, unweighted data from Cohort A+C of MonumenTAL-1 have been provided in company Table 1. The hazard ratio (HR) for progression free survival (PFS), overall survival (OS) and time to discontinuation (TTD) results are reasonably consistent visually with the initial company submission which included only Cohort C. The EAG highlight previous clinical expert comment which stated that "Cohort C (0.8 mg/kg SC every two weeks) most likely reflects anticipated UK practice as "*patients would need to spend less time at the treatment centre*"."

The company state that the Cohort A+C ITC result is not used in the company base case. However, the company have provided 10:90 weighted A+C as a scenario analysis as requested by committee – the EAG confirm that the results are consistent with the company base case. Please see EAG confidential appendix for details.

Company DGD Table 1. 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)

Comparison	Naïve (pooled, unweighted Cohort A+C)	Adjusted		
		ATT (Cohort C)	ATT (pooled, unweighted Cohort A+C)	ATT (pooled, 10:90 weighted Cohort A+C)
PFS				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
OS[a]				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
TTD				
HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

p-value	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: [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.
Abbreviations: ATT: average treatment effect for the treated population; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.

Comment 2a: COVID-19 censored OS ITC analyses

A fundamental problem of the company's analyses is that the compared cohorts were unequally protected against COVID infection. The company have employed MajesTEC-1 outcomes from the teclistamab arm to compare with talquetamab. Assessment of the impact of the lack of vaccination for COVID in teclistamab recipients seems mandatory for a reliable comparison between treatments.

To address the potential impact of COVID on overall survival in monumentAL-1 and MajesTEC-1 the company undertook re-analyses censoring patients at time of COVID-related death and then conducted ITC using the new OS data. This represents only one of several avenues available to owners of detailed IPD of the population for assessing COVID impact and on its own is inadequate. Assessment of COVID-related death may be inaccurate and likely ignores long term prognosis of those who were infected but did not die from COVID.

Using the censoring approach changed the estimated hazard ration (HR) between comparators from [redacted] in the company's original ITT analysis to a base case value of [redacted]. The company additionally generated a HR of [redacted] using an *"alternative censoring approach"* to that employed in the base case. Considering the considerable difference in lack of vaccination in the MonumenTAL-1 population relative to MajesTEC-1 these increases in HR (reductions in relative advantage of talquetamab over teclistamab) seem modest and are likely to underestimate the full impact of COVID-19 in MajesTEC-1.

In particular, as indicated in their original report, the EAG mentioned a statement by the company from TA1015, which highlighted that among the [redacted] death events observed at the time of data-cut off within the teclistamab cohort, [redacted] were due to COVID, representing nearly [redacted] of all infection-related deaths in MajesTEC-1. In contrast, only [redacted] infection-related deaths occurred in the talquetamab group out of [redacted] death events (i.e. a maximum of [redacted] of covid-related deaths).
It is therefore surprising that, after censoring of COVID-related death events, the relative effect of teclistamab compared with talquetamab on OS is barely affected.

EAG understanding of the intended aim of teclistamab treatment in MajesTEC-1 was to estimate outcomes (vs. POMDEX) while guarding against extraneous infections. Protection from COVID was inadequate and therefore the *"intended treatment regimen"* was not received; this implies the company should endeavour to fully determine COVID impact. The main protection from infection was to use IVIg infusion *"as required"*. EAG understanding is that IVIg was not used as prophylactic for duration of treatment, contrary to the approach in two recent real world European studies. Protection from infection may have been inadequate on two counts: no vaccination vs. COVID, and lack of prophylaxis with IVIg.

Although an ITT analysis is generally a preferable approach, special circumstances arise with the COVID pandemic so that the unvaccinated majesTEC-1 trial population failed to receive *"intended treatment regimen"*. For a fuller understanding of the impact of COVID a treatment-received analysis is relevant. Because these patients did not receive the *"intended treatment regimen"*, ITT analysis may cease to be a justified analysis either with or without

censoring for COVID related death. The EAG is unable to undertake *"intended treatment regimen"* because requisite IPD is only available to the company.

With IPD additional avenues are available to the company to try and assess the impact of COVID in majesTEC-1. The company might report exploratory OS analyses using teclistamab patients who received COVID vaccination, compared to patients from the vaccinated talquetamab group; and or the company could compare OS between unvaccinated talquetamab patients and unvaccinated teclistamab patients.

Comment 2b: PFS2 analyses for Cohort C in MonumenTAL-1

The company maintain that relative to teclistamab, talquetamab improves immune fitness due to less compromised humoral immunity, consequently patients can fight infections more vigorously and be less susceptible to comorbidities associated with repeated infections.

The company conducted new progression-free survival (PFS) analysis (termed PFS2) to compare the progression-free status of patients taking account of impact of subsequent treatment; the stated aim was to provide an understanding of outcomes of patients' post-treatment (e.g. with talquetamab or teclistamab). Investigator-assessed progression was employed and new PFS defined as the time between the study treatment start date and date of event that was defined as *"progressive disease as assessed by investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first".*

The EAG would prefer that independent assessment rather than investigator assessment be employed in this new analysis. The company's new analysis yielded a treatment adjusted HR (talquetamab vs. teclistamab) of [redacted] (95% CI: [redacted], [redacted]) p=[redacted]).

The EAG doubt the new PFS comparison is equitable between arms because the teclistamab patients who then receive subsequent treatment (e.g., talquetamab) have been faced with the COVID-19 challenge *sans vaccine*, whereas talquetamab patients who receive other treatment (e.g., teclistamab) have not.

The EAG understanding from the company's description is that in the new analysis there was no censoring of patients who experienced COVID-related death. According to the definition of PFS defined above, it is possible that some deaths in the teclistamab arm occurring prior to observed progression and counted as progression event were in fact COVID-19 associated deaths and could have been censored rather than counted as events (see Table 2, cases of death due to progressive disease). The impact of this is difficult to ascertain.

Table 2. The number the causes of death due to progressive disease (PD)

Death, N (%)	**Talquetamab** **MonumenTAL-1 Cohort C (0.8 mg/kg Q2W) [N=154]**	**Teclistamab** **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[a]	[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[a]	[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)[b]	[redacted]% of those who died)[c]
Other	[redacted]% of those who died)[d]	[redacted]% of those who died)[e]

Since the company's proposition suggests teclistamab recipients are particularly susceptible to infection (due to *"compromised humoral immunity"*) the lack of COVID-19 vaccination in MajesTEC-1 and non-prophylactic use of IVIg appears highly relevant since they are relatively more susceptible to and threatened by extraneous infection relative to talquetamab recipients. As such, as in the consideration of OS, it might be reasonable to consider an analysis *"according to intended treatment received"*.

Comment 2c: Rationale for the OS benefit of talquetamab over teclistamab

In this comment the company posits that all ITC analyses, before and after COVID-19 censoring, and additional PFS2 analyses support the significant OS benefit in favour of talquetamab. Reasons for this OS benefit are multi-faceted [redacted]

For reasons itemised in the EAG response to comments 2A and 2B, in the EAG opinion is that the company overstate the case: PFS2 analysis seems inequitable between compared treatments and appears not to censor COVID-related death; adjustment for the impact of COVID in the teclistamab arm, for both OS and PFS, is uncertain and difficult to estimate, so that the split between pre-PFS and post-PFS survival (with differing utilities attached in cost-effectiveness analysis) remains problematical.

It is important to realise that the company's economic base-case talquetamab OS model, an AFT-loglormal model, was independent of talquetamab patients' observed mortality seen in MonumentTAL-1, and of any models based on that observed data. Rather, the economic model for talquetamab OS was grounded in the accelerated failure-time (AFT) lognormal model for teclistamab OS based on data from MajesTEC-1 that was not adjusted for COVID-related deaths. This model was additionally then calibrated to fit clinical expert predictions for survival at 10 and 15 years. To obtain a required talquetamab model the ITC HR of [redacted], obtained without adjustment for COVID-related deaths, was applied to the teclistamab OS calibrated lognormal to 15 years. After 15 years the extrapolated talquetamab model was obtained by making hazard in the talquetamab model equal to that in the teclistamab model.

In summary:

- The PFS2 analysis does not appear equitable between arms
- Although censoring for COVID-19 related death is a reasonable first step in estimating the impact of COVID, on its own it is inadequate. Additional investigations should be explored. Censoring as the only approach is at risk of underestimating of COVID's impact on talquetamab versus teclistamab, thereby favouring the former in economic analysis and potentially skewing the partitioning between pre progression and post-progression survival

Comment 3: SACT data for talquetamab and teclistamab

The company submitted a report produced in partnership by the National Disease Registration Service (NDRS) and NICE on 2nd October 2025 as a separate document. This was accompanied by a reference pack with two additional sources (Chesnaye 2021, Non-sharable list).

The NDRS/NICE report provides age, gender and overall survival data for 182 individuals receiving either teclistamab or talquetamab for RRMM. Following exclusions, 139 people

received teclistamab and 39 received talquetamab as of 5th July 2025. Three individuals received teclistamab followed by talquetamab and were included in both populations. Data is summarised in Table 3. Maximum follow up was 47.6 months for teclistamab and 25.4 months for talquetamab. The EAG have not analysed SACT talquetamab data because patient numbers are too small and follow up too short for meaningful inference; furthermore, the company's economic model employs teclistamab survival to develop a model for talquetamab OS (by applying a HR).

Table 3. Summary data of technology use provided by NDRS/NICE

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)		

The SACT teclistamab KM plot for OS is shown in Figure F1. The Kaplan-Meier analysis is characterised by a very long flat tail from about 20 to 48 months. At 24 months only 12% remain at risk.

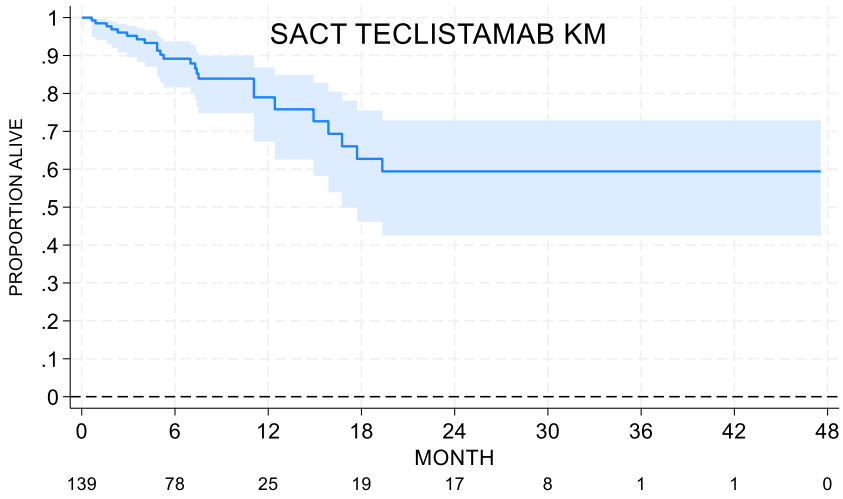

Figure 1 SACT OS of UK teclistamab treated patients (N 139); Kaplan-Meier analysis

The SACT submission fit eight parametric models to 48 months of KM, the reported AIC BIC values for models are reproduced in Table 4. Based on AIC BIC scores it is difficult to rank models because little separation exists in values for the various models, although Gaussian has a noticeably poor score.

Table 4 Information criteria values for SACT models (rounded to one decimal place)

Model	**AIC**	**BIC**

Exponential	240.8	243.8
Weibull	242.8	248.7
Lognormal	240.1	246.0
Loglogistic	240.4	247.3
Gaussian	271.7	277.6
Gamma	242.7	248.6
Generalised gamma	241.8	250.6
Gompertz	242.0	247.9

An alternative approach is to look at model extrapolations to a lifetime horizon and compare models with the company's clinical expert' estimate of survival at 10 and 15 years (10% and 3% respectively). EAG models extrapolated to 30 years are shown in Figure 2; these include Chen and Raleigh one parameter modes but do not include gamma or Gaussian models.

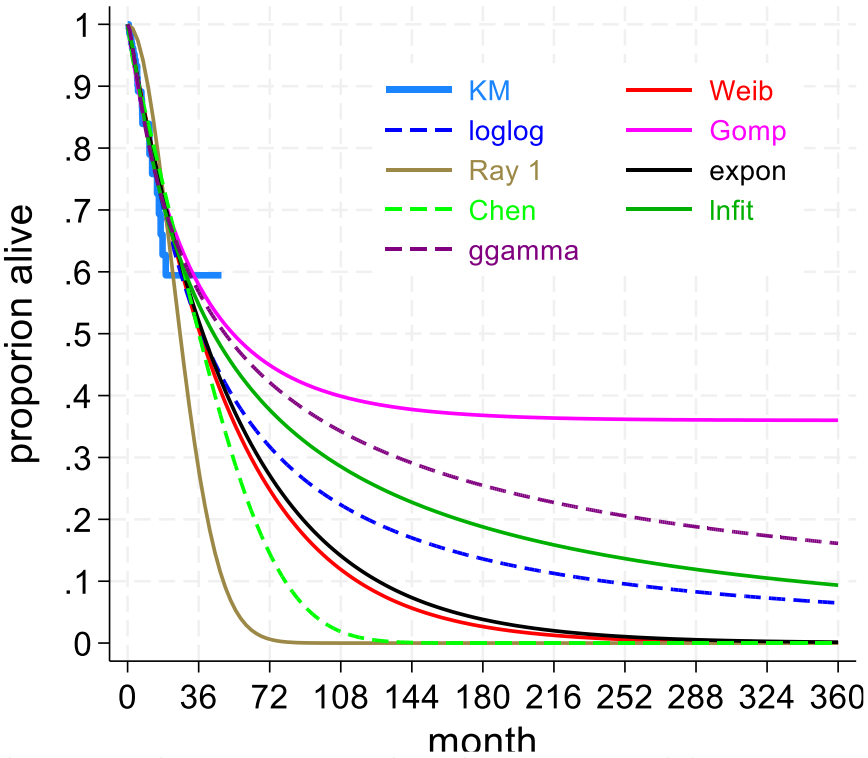

Figure 2 Extrapolation of models fit to SACT OS data. Weib =Weibull; loglog = loglogistic; Gomp = Gompertz; Ray 1 = Rayleigh one parameter; expon = exponential; lnfit = lognormal; ggamma = generalised gamma.

Parametric models have similar visual fit to the observed KM plot but generate very different extrapolation despite similar AIC BIC values. The various models give different weight to the KM flat tail. Some models with low AIC BIC values generate implausible extrapolation including Gompertz, ggamma, loglogistic and lognormal models. AIC BIC values are not a good guide to plausible extrapolation.

At 10- and 15-years Weibull and exponential models provide the nearest models to clinical experts' prediction of 10% and 3% survivors. Figure 3 shows the Weibull model extrapolated to the company life-time horizon of 40 years relative to clinical experts' prediction at 10 and 15 years.

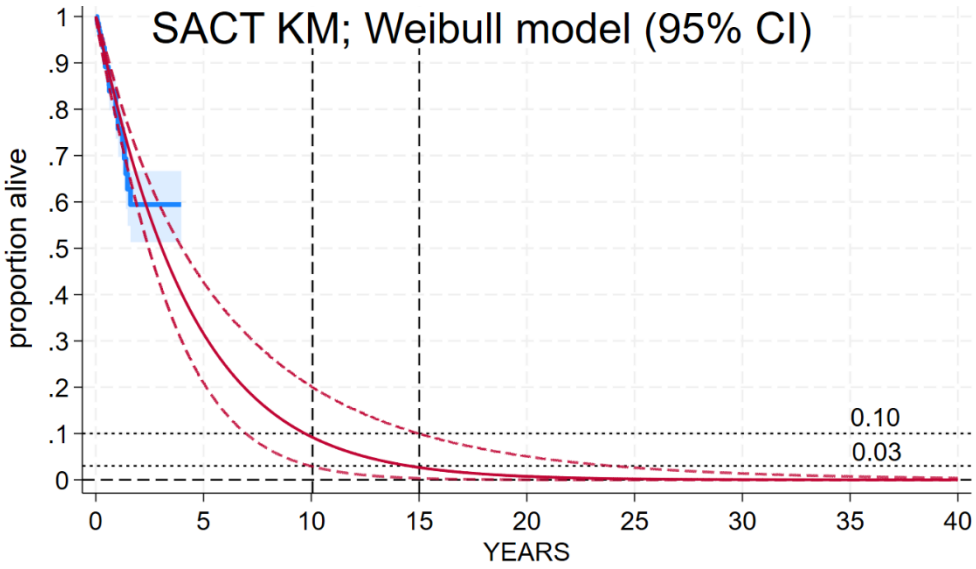

Figure 3 SACT Weibull models extrapolated to 40 years compared to clinical experts' prediction.

EAG exploratory analysis

The Perrot real-world study of French patients who received teclistamab treatment provides an alternative source of real-world OS. This study (N =303) is more than twice as large as SACT but provides data to maximum follow up of only 15 months. EAG models extrapolated to 25 years are shown in Figure 3.

As with SACT Gompertz, lognormal, loglogistic and generalised gamma models predict highly implausible survival in extrapolation. The Weibull model is the only parametric to conform to the company's clinical experts' opinion; the exponential model is pessimistic predicting no survivors beyond 10 years.

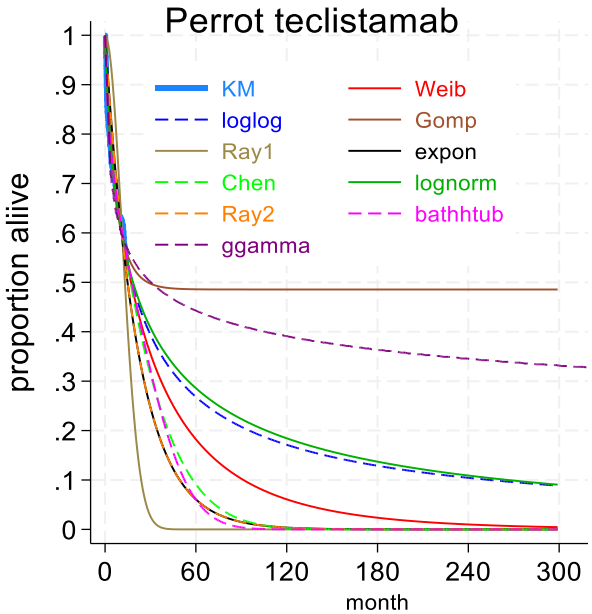

Figure 4 Extrapolation of models fit to Perrot OS data. Weib =Weibull; loglog = loglogistic; Gomp = Gompertz; Ray 1 = Rayleigh one parameter; expon = exponential;lognorm = lognormal; Ray 2 = Rayleigh two parameter; ggamma = generalised gamma.

Figure 5 shows the Weibull model extrapolated to the company life-time horizon of 40 years relative to clinical experts' prediction at 10 and 15 years.

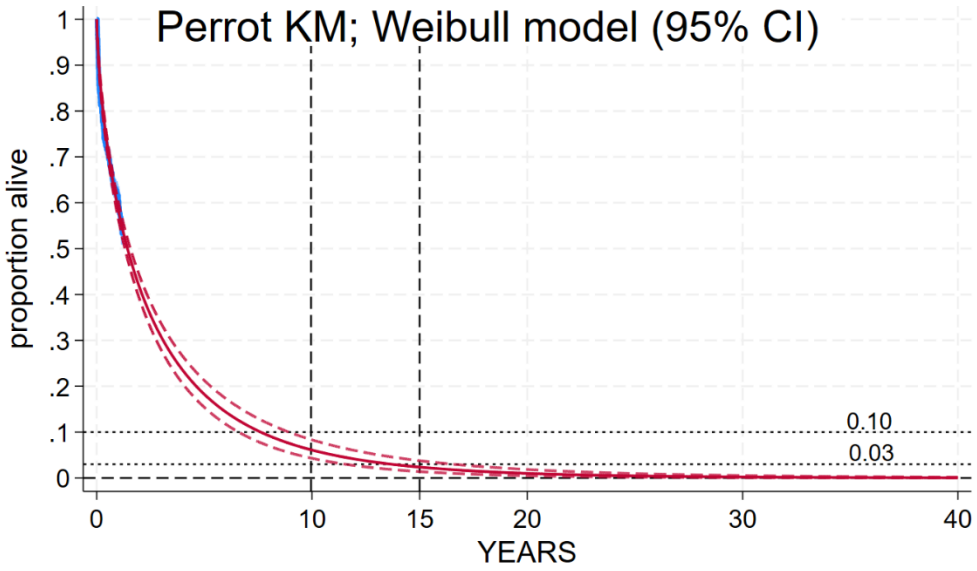

Figure 5 Perrot Weibull models extrapolated to 40 years compared to clinical experts' prediction.

Talquetamab

The copied SACT Talquetamab KM plot is shown below. As can be seen, fewer patients were available than for teclistamab and follow up was shorter.

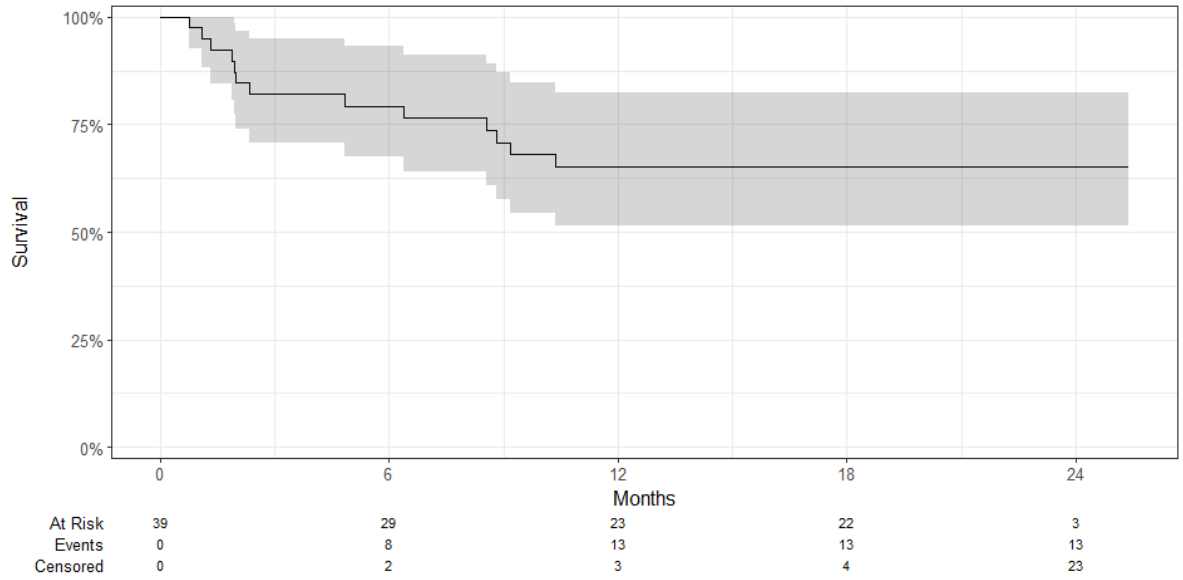

Figure 6.

Parametric models extrapolated to 40 years are shown in Figure 7.

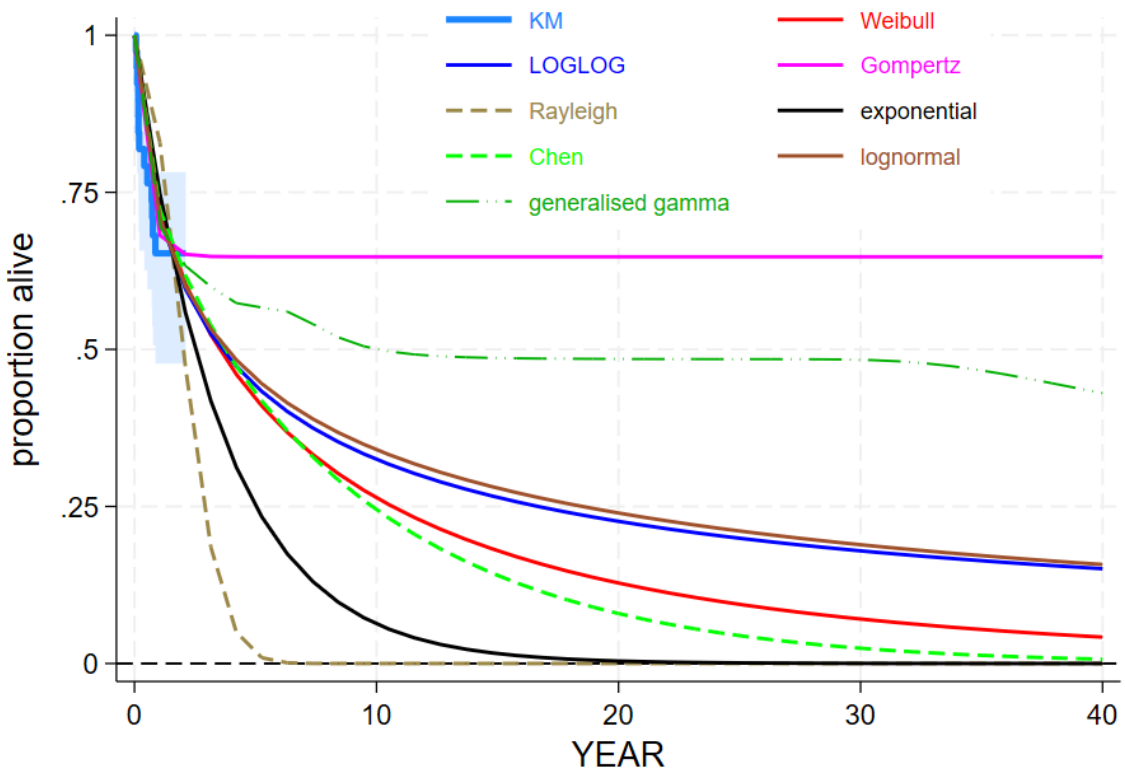

Figure 7 Talquetamab OS: Kaplan-Meier plot and parametric models.

Most models are implausible on extrapolation, including Gompertz, loglogistic, lognormal, Weibull and generalised gamma, they are strongly influenced by the long flat KM tail. The Rayleigh model is implausibly pessimistic. Only the exponential model delivers a plausible lifetime extrapolation. The talquetamab OS Weibull model is implausible in extrapolation: predicting 6.4% survivors at 40 years, the lifetime horizon of the company's economic model, and 4% and 3% remaining alive after 50 and 60 years respectively.

The talquetamab analysis may be compared with teclistamab to provide an estimate of the hazard ratio between arms of parametric models; in doing this, proportional hazards were assumed to hold as suggested in the company submission. In making comparison EAG considered exponential models to be most appropriate based on the principle of parsimony, and because exponential model for teclistamab provides an extrapolation that closely corresponds to clinical expert's predictions, and consideration of the plausibility of talquetamab models in extrapolation.

The SACT exponential models provide time constant hazards (lambda) of 0.022017 for talqueatamb and of 0.018876 for teclistamab, providing a hazard ratio of 0.852 in favour of talquetamab. This HR is more in line with the regression analysis by Etekal et al., of relapsed refractory MM than the ITC hazard ratios presented by the company of [redacted] and of [redacted] and [redacted] when censoring for COVID associated death.

Summary and conclusion

The SACT and Perrot analyses provide alternatives to the company's original estimate of teclistamab OS from MajesTEC-1 and to the company's more recent analysis based on MajesTEC-1 data modified by censoring for COVID-associated death.
Both real world studies are likely un-associated with problems from the COVID pandemic whereas for any OS models based on MajesTEC-1 to be reliable rigorous adjustment for lack of vaccination against COVID is required. EAG doubt that censoring for COVID-associated deaths is sufficient on its own to accomplish this.

All studies indicate that among many explored parametric teclistamab models exponential or Weibull models predict survival that corresponds most closely to the company's experts' opinion of survival. As such the two real-world studies offer alternative but very similar Weibull models to those provided by the company.
In EAG opinion all studies have deficiencies that will result in great uncertainty in their application for cost-effectiveness analysis.

- Reliability of real-world studies may be limited because of small numbers of patients in SACT or too short follow-up (e.g. in Perrot.)
- MajesTEC-1 requires reliable adjustment for impact of COVID on an unvaccinated population; it is doubtful this is achieved in the company's submissions by only censoring for COVID-related deaths.
- The SACT analyses provide time constant hazard ratio between modelled arms that is notably less favourable for talquetamab than the company's ITC hazard ratios, and consistent with the hazard ratios presented by Eketal et al., based on analysis of 16 studies of relapsed refractory MM.

Comment 4: Impact of COVID-19 censored ITC analyses on economic results

The post DGD company base case included the impact of COVID-19 censoring. The company updated their base-case to include the AC preferred assumptions and an updated ITC OS HR, which 'corrects for the impact of COVID'. The EAG have re-run the company's updated base-case, using the commercial agreements. Please see cPAS appendix.

However, the EAG question the validity of the ITC result for the covid censored patients (as discussed in EAG Comment response 2-3**).** The EAG have reservations about the new ITC OS HR.

Additionally, we have re-run the analyses for with the AC's preferred assumptions, with no change to the original HR. Please see cPAS appendix.

Company comment 5: Scenario analyses with independent extrapolations for talquetamab and teclistamab without calibration to clinical expert estimates

The company provided various modelling scenarios in their DGD (without company clinical calibration as per the initial submission). In their scenario analysis the company adopted the EAG base case Weibull extrapolation for the long-term survival outcomes for teclistamab (see comment 6).

The company note that modelling of efficacy outcomes using independently applied survival extrapolations leads to small increases in incremental costs, over the HR approach, for all scenarios explored. The EAG summarise these in the confidential appendix.

Company comment 6: Additional details on subsequent treatment adjustment methods *"Using alternate parametric distributions for the two-stage subsequent treatment adjustment has a negligible impact on the ITC results, thereby minimising any uncertainty with this adjustment"*

The company provided additional methodological detail of the methods used to adjust for subsequent treatments not available in NHS clinical practice. In Table 9 of the company DGD response, they provide acceleration factors and AIC values for alternative parametric distributions for their two-stage adjustment.

When exploring these alternatives, the company suggest that the OS HRs for treatment with talquetamab compared to teclistamab ranged from [redacted]95% CI: [redacted]) [Gamma] to [redacted] (95% CI: [redacted]) [LogNormal].

- The EAG agree with the company's conclusions that these results are visually consistent with original Weibull distribution. These results were consistent with the company's approach of using the Weibull distribution in the accelerated failure time (AFT) model thereby minimising any uncertainty with this adjustment.

In summary, it is not clear why the company appear to select an AFT Weibull rather than proportional hazards Weibull in view of the application of a time constant ITC hazard ratio. However, as the two Weibull models are visually consistent then this is plausible. The EAG consider this a minor issue relative to concerns regarding COVID non-vaccination adjustment only investigated via censoring.

Company comment 7: Inclusion of dysgeusia
The company have included the disutility associated with dysgeusia in their revised base case (company appendix 1).

Please see EAG confidential appendix for impact of this change on the ICER.

Company comment 8: Discussion of benefits captured in the model
No EAG response provided. This is company opinion with regards thresholds for committee decision making.