National Institute for Health and Care Excellence

Health Technology Evaluation

Linvoseltamab for treating relapsed or refractory multiple myeloma after 3 or more treatments [ID6609]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	GlaxoSmithKline	The topic and proposed evaluation route are appropriate.	No action required.
	Myeloma UK	No comments.	No action required.
	Pfizer Ltd	No comments.	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron believes the proposed evaluation route (i.e., STA) is appropriate	No action required.
Wording	GlaxoSmithKline	The wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider.	No action required.
	Myeloma UK	Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness.	No action required.

Section	Stakeholder	Comments [sic]	Action
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron believes the wording of the remit is appropriate	No action required.
Timing issues	GlaxoSmithKline	Considering the currently reimbursed treatments (and potential therapies currently undergoing appraisal), there are a number of effective therapeutic options in each of the lines of treatment in scope (1-3). In view of the fact the currently available data from registrational trials for linvoseltamab is in much later lines and out of scope of this appraisal (median 5 prior lines of therapy in NCT03761108) and the on-going trials in earlier lines not expected to reach primary completion till 2032, the urgency to the NHS should be considered low.	Thank you for your comment. No action required.
	Myeloma UK	No comments	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Despite the emergence of new NICE-recommended therapies, multiple myeloma (MM) remains an incurable disease in which all patients eventually relapse. There remains an urgent medical need for treatments that can achieve deep and durable responses, affording the opportunity for treatment-free intervals for patients with relapsed or refractory MM (RRMM) who have received ≥3 prior therapies (proteasome inhibitor [PI], an immunomodulatory drug [IMiD], and an anti-CD38 antibody [mAb]). The dosing of currently available bispecific antibodies is not yet optimised, with dosing being once weekly (de-escalating to once every two weeks in certain patients), and there is a need for a bispecific antibody with less frequent dosing as well as improved efficacy and lower cytokine release syndrome (CRS). Furthermore,	Thank you for your comments. No action required.

Section	Stakeholder	Comments [sic]	Action
		patients with triple-class exposed (TCE) RRMM indicate that they value treatment regimens that are tolerable and have a convenient dosing schedule[1-3]	
Additional comments on the draft remit	GlaxoSmithKline	N/A	No action required.
	Myeloma UK	No comments	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	GlaxoSmithKline	The background information is considered to be accurate and complete.	No action required.
	Myeloma UK	We consider this information to be sufficient and accurate.	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Linvoseltemab has been studied in a clinical trial as monotherapy in adult patients with relapsed or refractory multiple myeloma with progression on or after at least three lines of therapy including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody or are triple-class (PI/IMiD/anti-CD38) refractory.	Thank you for your comments. The scope has been updated to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	GlaxoSmithKline	The population is appropriately defined.	No action required.
	Myeloma UK	We consider the population to be appropriately defined. Despite approvals for treating myeloma in recent years given the heterogeneity of the disease an unmet need remains and there is a need for flexibility at each stage of the pathway. It is common in myeloma appraisals that final company submissions are narrower than full marketing authorisation. If the company seeks to pursue NICE approval for a narrower patient population than the final marketing authorisation it is vital that this reflects unmet need, current and likely future gaps in the pathway, and is not just driven by commercial considerations	Thank you for your comments. No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron believes that the population defined in the scope should reflect the proposed wording for the UK marketing authorisation, namely [redacted]	Thank you for your comments. The wording of the population section has been updated to align with the clinical trial.
Subgroups	GlaxoSmithKline	No subgroups suggested.	No action required.
	Myeloma UK	No comments	No action required.
	Pfizer Ltd	No comments	No action required.

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	Regeneron Pharmaceuticals Inc	Given the high unmet medical need and poor outcomes observed in later lines of MM treatment, Regeneron considers that linvoseltamab should be made available to all eligible patients, such that there are no additional subgroups which should be considered separately.	Thank you for your comments. No action required.
Comparators	GlaxoSmithKline	'Belantamab mafodotin plus pomalidomide and dexamethasone (subject to NICE evaluation)' and 'Belantamab mafodotin plus bortezomib and dexamethasone (subject to NICE evaluation)' have received technology appraisal guidance and final draft guidance respectively. • Neither treatment should be considered comparators 'for people who have had 3 prior therapies' or 'for people who have had 4 prior therapies' given they have received recommendations within the 2L RRMM setting. Ciltacabtagene autoleucel has not been included and is a prospective comparator (subject to NICE evaluation) • Ciltacabtagene autoleucel for treating relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 therapies [ID4012]	Thank you for your comments. The comparators have been updated.
	Myeloma UK	We agree that these are treatments available to this patient population. However, Myeloma UK believes that bispecifics teclistamab and talquetamab are the main comparators. We expect that final indication in the MHRA licence will match the EMA licence therefore livoseltamab will only be indicated for patients who have received at least three prior treatments, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, In current clinical practice it is our understanding that patients in this group and fit enough to recieve bispecifics, will receive: • Teclistamab • Elranatamab (via CDF) • Talquetamab	Thank you for your comments. At this early stage, all treatments have been retained to keep the scope broad to account for the marketing authorisation, and relevant in the event of potential changes including delays to the company submission. Comparators from evaluations in

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		• Clinical trial • Compassionate use / Early access scheme The combination of panobinostat plus bortezomib and dexamethasone is not widely used in clinical practice and should not be used as a comparator in this NICE appraisal. Daratumumab, lenalidomide and isatuximab containing combinations would not typically be used in this patient population due to drug resitance from previous exposure. They should not be used as comparators in this NICE appraisal. The belantamab mafodotin containing combinations are only approved for patients who have had one prior treatment and are not comparators for this appraisal. NICE appraisals for [mezigdomide with dexamethasone and carfilzomib] and [teclistamab plus daratumumab] have not started scoping and therefore should not be included as comparators in this appraisal. While selinexor plus dexamethasone (Sd) or pomalidomide plus dexamethasone (Pom-Dex) could be considered comparators at fifth line or beyond, our understanding is that both Sd and Pom-Dex are considered salvage/end of life treatments if a bispecific or clinical trial is suitable, it would be considered unethical to give Sd or Pom-Dex, considering their far shorter PFS and ORR. We therefore would not consider Pom-Dex a comparator at fourth line, or Sd/Pom-Dex at fifth line if bispecifics (teclistamab/talquetamab) are suitable.	development have been included, where applicable, and noted as “subject to NICE evaluation”. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant to its decision problem.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pfizer Ltd	**Comment 1** Please note elranatamab is currently in the CDF. It is mentioned in the draft scope page 2 but is **not** in the PICOS table. Please could this be added also. *"elranatamab after 3 or more lines of treatment including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody (NICE technology appraisal guidance 1023).* **Comment 2** Please could you review recommendation wording for all treatments to align with NICE website recommendations. For example, • NICE technology appraisal guidance 1015 recommends teclistamab as a treatment option for adults who have had at least 3 previous treatments. Should read, • Recommends teclistimab as an option for treating relapsed and refractory multiple myeloma in adults, only after 3 or more lines of treatment (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on the last treatment. • From our review the elranatamab and Isatuximab pomalidomide dexamethasone wording is also inconsistent with current NICE recommendation wording and should include its version of, "progressed on the last treatment".	Thank you for your comments. In line with section 2.2.15 of NICE technology appraisal and highly specialised technologies guidance: the manual which states that "Technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators", elranata mab was initially not included in the list of comparators. However, as TA1023 is under review in ID6653, elranatamab has now been added, subject to NICE evaluation. The background section of the scope provides a brief overview for the evaluation. Hyperlinks to the relevant

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		Comment 3 Please would it be possible to include a new section to align with the stated recommendation(s) and update PICOS table accordingly. For people who have had at least **2 prior therapies**: • NICE technology appraisal guidance 171 recommends lenalidomide plus dexamethasone as a treatment option for people who have had at least 2 prior treatments. • NICE technology appraisal guidance 380 recommends panobinostat plus bortezomib and dexamethasone as a treatment option for adults who have had at least 2 prior treatments including bortezomib and an immunomodulatory agent. Also based on the draft scope for ID6549 there seems to be a number missing from the 2 prior therapies list; • NICE technology appraisal guidance 870 recommends ixazomib plus lenalidomide and dexamethasone after 2 or 3 lines of treatment. This intervention is mentioned in the 3 prior treatments section of this scope but this is inconsistent with ID6549 and we are unclear which way round this should be but consistency across scopes would be welcome.	technology appraisal guidance have been included, where the full recommendation wording is available. Nevertheless, for consistency, the phrase “and the myeloma had progressed on the last treatment” has been added where relevant. The population for this appraisal is ‘adults with relapsed or refractory multiple myeloma who have had 3 or more previous treatments’. NICE TA974 is only recommended after 1 or 2 prior treatments, so is not considered a relevant comparator in a population with 3 prior treatments.

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		• NICE technology appraisal 974 NICE also recommends selinexor plus bortezomib and dexamethasone if the condition is refractory to lenalidomide (TA974).	
	Regeneron Pharmaceuticals Inc	Regeneron considers teclistamab (TA1015) and talquetamab (TA1114) as the most relevant decision comparators to linvoseltamab. Both teclistimab and talquetemab are recommended by NICE for routine commissioning as options for treating relapsed and refractory multiple myeloma in adults, only after 3 or more lines of treatment (including an IMiD, a PI and an anti-CD38 antibody) when the myeloma has progressed on the last treatment[4,5]. Clinical experts attending the first committee meeting for TA1114 confirmed that teclistamab was '*the most frequently used fourth-line treatment option for relapsed and refractory multiple myeloma'* in UK clinical practice. As a result, the committee concluded that '*teclistamab was the most relevant comparator to talquetamab for this evaluation'*[5]. Since the issuance of this guidance, Regeneron understands that there has been no change to clinical practice in the NHS in relation to the treatment pathway for 4L+ TCE RRMM, reaffirming teclistamab and talquetamab as most relevant decision comparators for this appraisal. This has further been validated by two leading clincians, practising in England, that confirmed that the most relevant comparators are teclistimab and talquetemab only. Based on the conclusions arising from the recent appraisals of 4L+ TCE RRMM technologies, namely teclistamab, talquetamab and elranatamab (TA1023; available through CDF), Regeneron does not consider the following	Thank you for your comments. The comparators have been updated. At this early stage, all treatments have been retained to keep the scope broad to account for the marketing authorisation, and relevant in the event of potential changes including delays to the company submission. Comparators from evaluations in development have been included, where applicable, and noted as "subject to NICE evaluation". The company will have the opportunity during the full evaluation to outline which comparators it considers to be most

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		treatments included in the NICE draft scope as relevant decision comparators for the appraisal of linvoseltamab: • **LenDex (TA171), IxaLenDex (TA870) and daratumumab (TA783)** were removed from the final scope of talquetamab (TA1114) based on committee conclusions of teclistamab (TA1014) and elranatamab (TA1023)[1]. Hence, Regeneron does not believe that these treatments should be considered as comparators and their inclusion in the final scope for this appraisal would create inequity. • **PomDex (TA427), PanoBorDex (TA380), and SelDex (TA970)** are not relevant comparators for this appraisal. These technologies are considered to have been displaced by teclistamab and talquetamab in the 4L+ TCE RRMM treatment setting in UK clinical practice, a view supported by clinical experts. Of note, PanoBorDex is not used in routine clinical practice in 4L+ as confirmed by the clinical expert submission for TA1114 and committee discussion in TA658 and TA783. • **IsaPomDex (review of TA658 [ID4067])** is not considered to be a relevant comparator for this appraisal. As highlighted during the scoping phase for talquetamab, RWE in the UK has demonstrated that over 95% of IsaPomDex patients are anti-CD38 naïve[6]. In addition, IsaPomDex is not currently recommended for routine commissioning in the UK; this technology is currently under evaluation by NICE following an appeal process • **BelPomDex (TA1133)** is not considered to be a relevant comparator for this appraisal. This technology has been recommended by NICE in the	relevant to its decision problem.

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		2L+ positioning, hence it is anticipated to be used earlier in the treatment pathway than the 4L+ setting and is does not represent a relevant comparator for TCE RRMM patients in UK clinical practice. • **BelBorDex (GID-TA11203)** is not considered to be a relevant comparator for this appraisal. This technology is currently undergoing appraisal by NICE in the 2L+ positioning; hence it is anticipated to be used earlier in the treatment pathway then the 4L+ setting. Therefore, this technology is not a relevant comparator for TCE RRMM patients in UK clinical practice. • **Teclistamab plus daratumumab (GID-TA11162)** is not considered to be a relevant comparator. This technology is pending NICE guidance and will not be available for routine use in the NHS at the time of submission. • **Mezigdomide with dexamethasone and carfilzomin (GID-TA11660)** is not considered to be a relevant comparator. This technology is pending NICE guidance and will not be available for routine use in the NHS at the time of submission.	
Outcomes	GlaxoSmithKline	The outcomes listed are appropriate.	No action required.
	Myeloma UK	Yes	No action required.

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	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron believes the outcomes listed are appropriate.	No action required.
Equality	GlaxoSmithKline	No equality issues identified.	No action required.
	Myeloma UK	No comments	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron is not aware of any potential inequality issues.	No action required.
Other considerations	GlaxoSmithKline	The high rates of hypogammaglobulinemia with BCMA-directed BsAb and consequent infections, support universal use of immunoglobulin (IG) replacement therapy.[1] The service impact arising from this should be considered, in particular the cost and administration burden. In the UK, the national shortage of intravenous IG should also be considered as an access barrier in this context.[2] References: [1] Garfall, A. L., E. A. Stadtmauer. Understanding Infection Risk with Anti-BCMA Bispecific Antibodies. Blood Cancer Discovery: OF1-OF3. In 2023.	Comments noted. The company will have an opportunity to outline the benefits of the technology in its submission. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		[2] Immunodeficiency [Internet]. 2020 [cited 2023 Oct 23]. Available from: http://www.immunodeficiencyuk.org/	
	Myeloma UK	No additional suggestions	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	Regeneron does not have other considerations to be raised.	No action required.
Questions for consultation	GlaxoSmithKline	N/A	No action required.
	Myeloma UK	**Where do you consider linvoseltamab will fit into the existing care pathway for relapsing or remitting multiple myeloma?** We consider that linvoseltamab would be considered at fourth line, alongisde teclistamab and talquetamab. Patients are acutely aware as they move further and further through the pathway that achieving long periods of deep remission becomes increasingly difficult. Bispecifics have a vital role to play here in providing patients with treatment options that have long, durable periods of remission and therefore will be used at the earliest opportunity. **Would linvoseltamab be a candidate for managed access?**	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		We believe that linvoseltamab would be a candidate for managed access, the clinical trial is ongoing with data on progession free survival and overall survival still being collected. **Do you consider that the use of linvoseltamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Myeloma remains incurable and even after successful treatment, almost all patients eventually become resistant to existing treatments. New drugs and treatment approaches are urgently needed to overcome treatment resistance. While there is a bispecific antibody with the same mechanism of action approved, indirect comparison with linvoseltamab suggest that linvoseltamab may offer significantly improved progression-free survival, overall survival, and higher minimal residual disease negative results than other BCMA bispecifics (Lee et al 2025[1]). Linvoseltamab may also be given less frequently (every 4 weeks) after a period of initial treatment (24 weeks), compared with weekly dosing until at least 6 months (at which point, a patient may move to fortnightly dosing) for teclistamab, and the fortnightly dosing of talquetamab (after step up treatment has been completed). The less frequent dosing of linvoseltamab may offer a distinct social, financial, practical and psychological QoL advantages to patients through subsantially fewer hospital trips for treatment.	
	Pfizer Ltd	No comments	No action needed.

[1] Lee, H et al (2025). Indirect Comparison of Linvoseltamab versus Teclistamab for the treatment of triple-class exposed relapsed/refractory multiple myeloma. Available at: Indirect Comparison of Linvoseltamab Versus Teclistamab for the Treatment of Triple-Class Exposed Relapsed/Refractory Multiple Myeloma - ScienceDirect, last accessed 14/04/2025

Section	Consultee/ Commentator	Comments [sic]	Action
	Regeneron Pharmaceuticals Inc	**Where do you consider linvoseltamab will fit into the existing care pathway for relapsing or remitting multiple myeloma?** Linvoseltamab would add to the existing 4L+ TCE RRMM treatment landscape as an option for patients who have received at least three prior lines of therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. Linvoseltamab is to be prescribed in secondary care with routine follow-up in secondary care, which aligns with the delivery of other bispecific antibodies. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** As alluded to above, teclistamab and talquetamab are prescribed in secondary care with routine follow-up in secondary care. Subsequent treatments are also prescribed in secondary care with routine follow-up in secondary care. **Would linvoseltamab be a candidate for managed access?** Regeneron consider linvoseltamab to be a candidate for managed access. However, the company is seeking to achieve the routine commissioning of linvoseltamab in 4L+ TCE RRMM without the requirement of managed access.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of linvoseltamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Linvoseltamab represents the first bispecific antibody targeting both BCMA and CD3, bringing the patient's T-cells in close proximity to cancer cells and promoting their destruction. The availability of an alternative treatment option with a novel mechanism of action would be beneficial to patients and may not be captured in the QALY calculation. Furthermore, the dosing schedule for linvoseltamab may enhance patient convenience when compared with alternative bispecific antibodies[7,8], with a quicker transition to once every two weeks (Q2W) dosing for all patients and ability for once every 4 weeks (Q4W) dosing if ≥ very good partial response (VGPR) after 6 months[9]. This can meaningfully reduce travel and carer time for patients once they are stabilised. Additionally, fewer and shorter visits with linvoseltamab in deep response may ease capacity constraints on the healthcare system, indirectly benefiting other patients. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Data will be supplied from the Phase 1/2 LINKER-MM1 study.	

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Additional comments on the draft scope	GlaxoSmithKline	No comments	No action required.
	Myeloma UK	No comments	No action required.
	Pfizer Ltd	No comments	No action required.
	Regeneron Pharmaceuticals Inc	No comments	No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Takeda UK Ltd
Sanofi