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Dear Dr Chakravarty,

4th August 2023

**Appeal against the Final Draft Guidance (FDG) Issued by The National Institute for Health and Clinical Excellence (NICE) on 21st July 2023 for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more prior therapies [ID2701]**

# Executive summary

GSK is advancing an appeal under Ground 1a (NICE has failed to act fairly) and Ground 2 (unreasonableness) of the grounds permitted in accordance with NICE’s Guide to Technology Appraisal Appeal Process.

**Ground 1a (NICE has failed to act fairly)**

1(a).1 The Committee’s conclusions on the validity of belantamab UK RWE and related analyses lack transparency and are inconsistent with the focus placed on real-world data use in the NICE strategy for 2021 to 2026.

1(a).2 The Committee’s decision that belantamab is not suitable for use through the Cancer Drugs Fund (CDF) is procedurally unfair.

1(a).3 The Committee’s conclusion that TA897 should not be taken into account in the context of this evaluation is inconsistent with NICE’s processes and is inadequately explained.

1(a).4 The Committee’s conclusion that it would not recommend belantamab in the 5L+ TCR MM post-POM setting due to the uncertainty in the comparative evidence is unfair, given that these limitations were largely driven by the paucity of evidence for the comparator despite being recommended by NICE and in circumstances where the effect of the decision is that patients will be forced to receive less effective treatment with less evidence of benefit.

1(a).5 The Committee has failed to fairly consider belantamab in the original (5L+ TCR) or revised positioning (5L+ TCR post-pomalidomide subpopulation) in which belantamab offers significant benefits to UK patients with a high unmet need.

**Ground 2 The recommendation is unreasonable in the light of the evidence submitted to NICE.**

2.1 The Committee’s conclusion in relation to the data from the DREAMM-3 are unreasonable in the light of the evidence submitted.

2.2 The Committee’s failure to recognise belantamab as an innovative intervention with benefits not captured in the economic modelling is inconsistent with the innovation passport granted by MHRA, the evidence submitted by GSK and stakeholders’ comments in response to the consultation on the draft guidance and is therefore unreasonable.

2.3 The Committee’s conclusions on the severity modifiers in the 5L+ TCR post-POM subgroup are unreasonable given the evidence indicating the applicability of a 1.7 severity weight.

# Introduction

The following sections provide background information in relation to multiple myeloma and belantamab in order to assist the Appeal Panel. This summary is not intended to replace the more detailed information provided by GSK in the appraisal documents.

## Multiple Myeloma (MM)

Multiple myeloma (MM) is an orphan, incurable, progressive, malignant plasma cell disease, characterised by the abnormal proliferation of clonal B-cells in the bone marrow.1 It accounts for approximately 2% of all new cancer cases, with an estimated 5,951 new cases of MM in the UK each year, and an estimated 3,098 deaths.2,3,4 Patients aged 75 and over represent 43% of all new UK myeloma diagnosis with a median age at presentation of 72.6 years.2,5 Older patients are more likely to have comorbidities, such as cardiovascular disease and renal insufficiency, which may exclude use of certain treatments due to toxic side effects.6

The clinical course of the disease, although variable, typically includes periods of treatment and remission separated by inevitable relapses.7 Relapsed refractory MM (RRMM) is defined as disease that becomes non-responsive while on therapy or that progresses within 60 days of the last treatment in patients who previously achieved minimal response (MR) or better on prior therapy.8,9 A major challenge in MM is the evolution of the cancer and the build-up of resistance to different class of therapies as the disease progresses.10

It is important to note that populations considered in this appraisal, namely fifth line plus and triple class refractory (5L+ TCR) MM and the post-pomalidomide (post-POM) subpopulation, represent late lines of the disease management pathway that only a very small proportion of patients diagnosed with MM will reach. For example, Rabb et al. have shown that only 3% of patients diagnosed with MM reach 5L treatment according to a 2015 chart review describing real-world MM treatment patterns and outcomes in Europe.11

## MM treatment pathway

The treatment pathway for the treatment of MM recommended by NICE is complex and evolving.

MM patients who are refractory to the three established pillars of MM treatment, namely to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody (mAb) are referred to as TCR. In the 5L+ TCR MM setting, treatment options are extremely limited, with the result that patients face a very poor prognosis and feel abandoned.

Indeed, while NICE recommends interventions in broad populations which include the 5L+ space, there are currently no interventions specifically approved for 5L+ TCR MM patients. In this setting, the limited options typically consist of:

1. Pomalidomide in combination with low-dose dexamethasone (PomDex), is recommended as an option for treating MM in adults at third or subsequent relapse; that is, after 3 or more previous treatments (i.e., 4L+) including both lenalidomide and bortezomib (NICE TA427)12
2. Panobinostat in combination with bortezomib and dexamethasone (PanoBorDex) is recommended within its marketing authorisation, as an option for treating MM, that is, for ‘adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens (i.e., 3L+) including bortezomib and an immunomodulatory agent (NICE TA380)13
3. Inclusion in a clinical trial and/or an early access/compassionate use scheme, although this is typically restrictive due to the nature of corresponding inclusion and exclusion criteria.
4. Chemotherapy-based palliation in the absence of any alternative options.

For 5L+ TCR patients who have been exposed to pomalidomide (5L+ TCR post-POM) options are restricted to (2), (3) or (4), described above. Feedback from UK clinical experts suggests that the behaviour driving the use of PanoBorDex is one of desperation in view of the lack of alternative effective options and the poor survival outcomes in the context of toxicities associated with the PanoBorDex regimen.

## Unmet need

By the time MM patients reach 5L within the NICE treatment pathway, most will be TCR as they will have been exposed to and become refractory to a PI, an IMiD and an anti-CD38 mAb.14

Due to the disease pathophysiology, recycling of existing therapies in RRMM has limited efficacy as patients are re-exposed to treatments or classes of agents that they have previously developed resistance to.15

This emphasises the high and urgent unmet medical need for therapies that have a novel mechanism of action which can extend survival, bring hope to patients and offer clinicians an increased flexibility in earlier treatment decisions by adding a new treatment option in the 5L+ TCR MM treatment pathway.14 In the 5L+ TCR post-Pom setting, the unmet need for treatment options is even greater.

The extent of the unmet need is further evidenced by the increased uptake observed in the Company's data for the use belantamab through the NPP; in June 2023 alone, there were 23 NPP requests for belantamab. The total number of patients treated with belantamab through the NPP is 319 and the total number of requests is 623 (as of end of June 2023).

The unmet need for 5L+ TCR patients is confirmed by comments from the UK Myeloma Forum (UKMF) during the consultation on the draft scope: “This [appraisal] is urgent – there is a need to rapidly introduce effective therapies to help prolong disease control and overall survival. Importantly this [is] for a group of patients that have limited treatment options. This is evidenced by [the] considerable uptake of the belantamab compassionate use programme”. There is therefore a need to broaden access to belantamab in the NHS to help improve outcomes for a group of patients that have limited treatment options.

## Belantamab

Belantamab is a humanised IgG1κ monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF). It was granted a conditional marketing authorisation by the European Commission on 25 August 2020. This was automatically converted to a Great Britain conditional marketing authorisation on 1 January 2021, following the end of the transition period after the withdrawal of the UK from the EU. The licensed indication for use of belantamab is:

“…monotherapy for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least one proteosome inhibitor, one immunomodulatory agent and an anti-CD38 monoclonal antibody and who have demonstrated disease progression on the last therapy”.

Belantamab binds to cell surface B-cell maturation antigen (BCMA)16 which is present at high levels on MM cells, but is rarely expressed on most other cells aside from plasmablasts and differentiated plasma cells.17–20

Belantamab binds to cell surface BCMA and is rapidly internalised. Once inside a tumour cell, the cytotoxic agent is released, leading to cell cycle arrest and apoptosis. The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells.16

Due to the selective expression of BCMA, belantamab is an effective therapeutic option for the treatment of 5L+ TCR.21

According to the 2021 EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up of myeloma, belantamab is only one of 2 suitable options for TCR patients. (The other option, Selinexor with dexamethasone, has not been recommended by NICE.)22

## Procedural history of the appraisal

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| **Date** | **Event** |
| 01 June 2022 | Scoping commenced |
| 01 June 2022 - 01 July 2022 | Consultation on suggested remit, draft scope and provisional stakeholder list of consultees and commentators |
| 01 June 2022 | Invitation to participate |
| August 2022 | Final scope issued |
| 06 October 2022 | GSK submission to NICE |
| 24 October 2022 - 7 November 2022 | Clarification questions |
| 13 December 2022 | Evidence Assessment Group (EAG) report prepared by Warwick Evidence |
| 17 January 2023 - 14 February 2023 | Technical Engagement |
| 13 April 2023 | First Appraisal Committee meeting |
| 09 May 2023 - 31 May 2023 | Consultation on the Draft Guidance (DG)  |
| 31 May 2023 | GSK response to the DG |
| 14 June 2023 | Second Appraisal Committee meeting |
| 14 July 2023 | Final Draft Guidance (FDG) |

# Grounds of Appeal

## Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly.

### The Committee’s conclusions on the validity of belantamab UK RWE and related analyses lack transparency and are inconsistent with the focus placed on real-world data use in the NICE strategy for 2021 to 2026.

1. **The Committee’s conclusion that the UK RWE considered in this evaluation is subject to “potential bias” and confounding associated with the UK RWE for belantamab are not clearly evidenced and justified.**

The Committee’s assessment of the UK RWE evidence submitted in this evaluation is set out in section 3.8 of the FDG, resulting in the Committee’s conclusion:

“The committee agreed that the extent and direction of the potential bias was unclear in the company’s naïve comparison. It concluded that the company’s updated naïve comparison lacked validity and added further uncertainty around the efficacy of belantamab compared with pomalidomide plus dexamethasone.”

The UK RWE considered by the Committee comprised data from a retrospective non-interventional evaluation of belantamab in the UK, used in accordance with its licenced indication (the NPP study) and a descriptive, retrospective, non-interventional study of pomalidomide plus dexamethasone and using routine, patient level data from the NCRAS dataset (the NCRAS study). The UK RWE therefore reflects the use of both belantamab and pomalidomide plus dexamethasone as they are, in fact, used in clinical practice in the UK. Nevertheless, the Committee criticised the data and the comparison submitted by GSK:

“It [the Committee] noted that the median progression-free survival was much longer in the NPP study than in DREAMM-2. The Committee considered that this suggested that the population in NPP may be less likely to have disease progression and that this may favour belantamab in the company’s updated naive unadjusted comparison.”

However, the key consideration is not whether the population in the NPP study is less likely to have disease progression than the population in DREAMM-2, but rather whether the population in the NPP study reflects the patients likely to receive belantamab in UK clinical practice (which it clearly does) and whether it is appropriate to compare patients from the NPP study with those from NCRAS.

The Committee had previously referred to DREAMM-2, stating “the study included 58 centres, 7 of which included a very small number of people from the UK” (section 3.4 of the FDG). The issue of UK representation was therefore addressed by use of RWE from the NPP study, which was entirely based on UK clinical practice, rather than within the constraints of a clinical trial.

In terms of comparison between the NPP study and NCRAS, as documented in section 3.8 of the FDG, “the committee discussed whether the people having belantamab in the NPP were likely to be different to those having pomalidomide plus dexamethasone in the NCRAS study” and, following explanation by the clinical experts, they concluded “any differences between the populations would be minor”. GSK further explained that, to the extent that the comparison was subject to bias, this would operate against belantamab because “progression-free survival [in the pomalidomide plus dexamethasone group] would probably be overestimated by using a proxy measure (Time To Next Treatment, TTNT)”.

The Committee therefore has provided no explanation (a) for its conclusion that GSK’s comparison of data from the NPP study with NCRAS is likely to be biased in circumstances where the NPP study reflects UK data from real world clinical practice (explaining any difference from a formal trial with only a small number of UK participants) and/or (b) for its conclusion that the naive comparison of two UK RWE datasets is potentially biased and lacked validity, disregarding the views of the clinical experts in relation to the similarities between the NPP study and NCRAS. Rigorous and transparent decision-making is an essential requirement of procedural fairness and is recognised in NICE’s processes. In the NICE guidelines for health technology evaluations (2022).23 Section 6.1.8 provides:

“The credibility of the guidance produced by NICE depends on the transparency of the committee’s decision-making process. The committee’s decisions must be explained clearly with reference to all the available evidence, the contributions of experts, and comments received during consultation. The reasoning for the committee’s decision will be explained, with reference to the factors that have been considered, in the committee discussion section of the guidance.”

The standards set out at section 6.1.8 have not been met, with the result that the basis for the conclusions reached by the Committee in relation to use of UK RWE is unexplained, and GSK is unable to understand the Committee’s reasons for rejecting the naïve comparison.

1. **The rejection of the UK RWE as a basis for decision-making in the current evaluation is inconsistent with commitments made by NICE at the heart of its 2021 – 2026 strategy.**

The importance of RWE is a key focus in the NICE 2021 - 2026 strategy which states under the 4th pillar of the strategy, “We will be scientific leaders driving the research agenda across health and social care and thought leaders at the forefront of developing innovative approaches to using real-world data and data analytics to inform all aspects of our work”.24

Furthermore, the strategy describes the need to integrate real-world data into evaluation processes to inform rapid but robust decisions aiming to speed up access to new and effective treatments and embrace innovation.

In view of increasing recognition given to use of RWE, including in the NICE 2021-2026 strategy24, GSK prepared the naïve comparison based on UK RWE to support the evaluation of belantamab. However the Committee dismissed this analysis without adequate explanation (as set out above), simply accepting the EAG’s bald assessment: “the EAG considered that the company had not provided a valid reason for changing the efficacy source for belantamab from DREAMM-2 to NPP" GSK believes that, in line with the NICE 2021 – 2026 strategy24, this dataset, based on clinical use in a routine UK setting, should have been given more consideration to support patient access to an innovative medicine namely, belantamab. Any deficiencies, such as the immaturity of the data referenced at section 3.8, could readily be confirmed through a managed access agreement.

In conclusion, the approach to UK RWE is central to this evaluation, impacting not only the Committee’s conclusions on clinical effectiveness in section 3.8, but also its willingness to accept highly favourable assessments of cost-effectiveness in section 3.18. It is GSK’s firm view that the approach reflected in the FDG is procedurally unfair and that the Committee should be required further to explain its conclusion that the NPP study is subject to bias and the naïve comparison unreliable, in the context of the evidence referenced above and the principles set out in its 2021-2026 strategy.

### The Committee’s decision that belantamab is not suitable for use through the Cancer Drugs Fund (CDF) is procedurally unfair.

In section 3.19 of the FDG, the Committee considered a recommendation for use of belantamab with managed access.

1. **The Committee has not applied the correct test as set out in its process guide.**

The circumstances in which the Committee should consider a recommendation for use of a technology with managed access are set out at paragraph 6.4.6 of NICE Health Technology Evaluations: the Manual:

When a committee is unable to recommend a medicine because there is still significant resolvable uncertainty, it can make a recommendation for further evidence to be gathered subject to managed access. The committee can consider a recommendation with managed access when:

* the medicine has not been recommended, it has the plausible potential to be cost effective at the currently agreed price, but the evidence is currently too uncertain, and
* new evidence that could sufficiently support the case for recommendation is expected from ongoing or planned clinical trials, or could be collected from patients having the medicine in clinical practice, and
* these data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.

In relation to cost-effectiveness, the test is therefore that the medicine “has the plausible potential to be cost effective at the currently agreed price” but “the evidence is currently too uncertain”.

In considering belantamab however, the Committee imposed a requirement for managed access that it should be presented with “a plausible reliable cost-effectiveness estimate”, referring to the reasoning applied for consideration of the product for routine use. The word “reliable” does not appear in the Manual in the context of managed access; its inclusion in the test applied by the Committee, contradicts the entire purpose of managed access, which is to provide a recommendation where the data are uncertain and therefore, by definition, not sufficiently reliable to support a recommendation for routine commissioning.

1. **The Committee’s apparent conclusion that only comparative data could sufficiently support the case for recommendation disregards the benefits of RWE.**

In relation to evidence to support the case for recommendation, the Committee stated at section 3.19:

“It also discussed that additional data collection would be unlikely to resolve the uncertainty around the efficacy of belantamab compared with the relevant comparators for this evaluation. Overall, the committee concluded that managed access was not a feasible option”.

While GSK accepts that managed access will not generate comparative data, we consider that the data generated through managed access will supplement the significant evidence of belantamab efficacy already presented to the committee throughout this evaluation, including data from a single-arm trial (DREAMM-2) and RWE from belantamab use (the NPP study), in UK clinical practice. This cumulative dataset would clearly address most if not all of the uncertainties identified by the Committee in the FDG:

* Firstly, the collection of additional UK RWE would likely confirm the findings from the UK NPP study including the evidence of progression free survival and also increase the sample size, thereby addressing two concerns raised by the Committee (section 3.8 of the FDG);
* Secondly, the collection of additional UK belantamab RWE through a managed access agreement would allow the generation of data with a longer follow-up than the NPP study and will increase the number and quality of the baseline characteristics which will also address criticisms by the Committee and improve the reliability of indirect treatment comparisons (ITCs) with the NCRAS dataset.

Incidentally, the MM pathway evolves rapidly, and it is likely that at the end of the managed access agreement, the sample size of the NCRAS cohorts would have increased, which would also improve the quality of ITCs.

In conclusion, GSK believes that a CDF recommendation will allow the resolution of the areas of uncertainty identified by the Committee in addition to providing patient access to an intervention with demonstrated efficacy outcomes.

### The Committee’s conclusion that TA897 should not be taken into account in the context of this evaluation is inconsistent with NICE’s processes and is inadequately explained.

At section 3.3 of the FDG, the Committee refers to TA89725 (daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma; managed access review of TA573) and states that this “may affect the treatment pathway at later lines but that it would likely be some time before these changes would happen in clinical practice.” The Committee stated that TA897 was published after consultation of the guidance for the evaluation of belantamab closed and concluded “because of this, it agreed that it could not take the consequences of this update to the treatment pathway into account in its decision making”.

The purpose of NICE’s guidance is to issue recommendations to the NHS that will be of use in guiding treatment decisions. This exercise is futile if the guidance issued by NICE is outdated before it has even been finalised. NICE has substantial discretion to consider comparators and product positioning in cases where the treatment landscape is changing, and it is unfair and contrary to NICE’s own procedures not to do so.

NICE’s procedures do not specify that the cut-off for considering the impact of treatment changes is the end of consultation on preliminary draft guidance and it is unclear why the Committee appeared to consider that this was the position, when drafting the FDG. In this case however in particular, the FDG on daratumumab with bortezomib and dexamethasone had been made public on 24 April 2023 and the period for any appeal concluded on 8 May 2023, before the commencement of consultation on the ACD for belantamab on 9 May 2023. In circumstances therefore, where the content of TA897 was known to stakeholders prior to consultation on belantamab it was procedurally unfair for this information to be excluded from consideration by the Committee at its meeting on 14 June 2023. Nevertheless, NICE’s position on whether or not TA897 should be taken into account was confused and inconsistent, with advice issued to GSK before consultation that it could not be considered and differing views expressed by NICE and Committee members up to and during the second meeting of the Committee.

Fairness clearly requires that stakeholders have adequate opportunity to comment on draft guidance and if the treatment pathway changes so that such consultation has not taken place, it is incumbent on the Committee to hold a further meeting to ensure that guidance that is both relevant and subject to consultation takes place. There is no indication in the FDG that either NICE or the Committee gave any consideration to whether the publication of TA897 meant that a further period of consultation was necessary to consider its implications in the context of belantamab, to ensure that relevant guidance would be issued.

Finally, the Committee concluded “that it would likely be some time” before the changes resulting from TA897 would happen in clinical practice. The basis for this conclusion is unexplained and it appears inconsistent with the fact that daratumumab with bortezomib and dexamethasone has been accessed through the Cancer Drugs Fund and is therefore to some extent already established treatment. We are aware that NICE is committed to ensuring that its recommendations are implemented and its guidance is viewed as standard treatment to be considered in other evaluations; this means that TA897 should be reflected in NHS practice soon if not with immediate effect. Furthermore, if it is in fact correct that TA897 will not be implemented for some time, this would presumably mirror any implementation of guidance for belantamab. GSK therefore contends that failure to take into account TA897 in the context of the current evaluation was procedurally unfair and has the result that NICE’s guidance will be irrelevant before it is even published.

### The Committee’s conclusion that it would not recommend belantamab in the 5L+ TCR MM post-POM setting due to the uncertainty in the comparative evidence is unfair, given that these limitations were largely driven by the paucity of evidence for the comparator despite being recommended by NICE and in circumstances where the effect of the decision is that patients will be forced to receive less effective treatment with less evidence of benefit.

In section 3.11 of the FDG, the Committee considered the evidence submitted by GSK in relation to use of belantamab in 5L+ TCR MM patients who had previously received treatment with pomalidomide. The Committee noted submissions by GSK that there was no clinical trial evidence for current standard treatment PanoBorDex in the relevant patient population and “recognised that efficacy outcomes for panobinostat plus bortezomib and dexamethasone were likely to be poor in this population”. However, the Committee then concluded “that it had not been presented with sufficient evidence to confirm that belantamab is more clinically effective than panobinostat plus bortezomib and dexamethasone at a population level”.

PanoBorDex was recommended by NICE in 2016 as an option for treating adult patients with RRMM who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent (TA380).13 While the recommendation in TA380 enables patients within the 5L+ TCR MM setting to access PanoBorDex, there was no evidence reported in TA380 supporting the efficacy and cost-effectiveness of this intervention as fifth line treatment. The rapid evolution of the MM pathway means that the unmet need increases as patients become refractory to multiple class of agents earlier in the pathway. At the time of PanoBorDex appraisal, anti-CD38 monoclonal antibodies were not yet available in NHS routine commissioning, thus PanoBorDex was used earlier in the treatment pathway and there was no evidence for use in 5L+ TCR MM.

To address this limitation, GSK performed a systematic literature review and a study of the NCRAS dataset to collect evidence for PanoBorDex efficacy in the 5L+ TCR MM post-POM population. No evidence was retrieved from the literature search and the cohort of patients in the NCRAS study was small, as would be expected for a heavily pre-treated group. These issues translate into significant challenges when attempting to perform an ITC of belantamab vs PanoBorDex in a 5L+ TCR MM population post-POM.

In conclusion, this issue not only reflects the difficulties associated with appraisals towards the end of the MM treatment pathway where patient numbers are small, and data are scarce, but also the challenges emerging as a result of previous recommendations made by NICE in broad populations (e.g., third line treatment and above) which limit access to future interventions in narrower subpopulations at later lines.

In the above circumstances, the inflexible approach of the Committee to the available data for PanoBorDex in the 5L+ TCR MM post-POM population is unfair. PanoBorDex is currently used to treat the 5L+ TCR MM post-POM population as recommended by NICE, but without supporting data, thereby excluding other treatments where data in 5L+ are available. The effect of an approach which penalises technologies such as belantamab for the fact that data for PanoBorDex are not available is that patients are forced to continue to receive treatment where there is limited supporting efficacy data and newer treatments where there is evidence of superior benefit cannot be accessed.

### The Committee has failed to fairly consider belantamab in the original (5L+ TCR) or revised positioning (5L+ TCR post-pomalidomide subpopulation) in which belantamab offers significant benefits to UK patients with a high unmet need.

In section 3.10 of the FDG, the Committee referred to the DREAMM-3 clinical trial and recognised that belantamab may offer benefits to some individuals with 5L+ TCR MM, but that it was not possible to define this subgroup of people who would be expected to have greater clinical benefit than the broader eligible population.

As per the current NICE pathway, there are no approved therapies with a validated biomarker to predict which patients may respond to therapy. Therefore, the Committee’s comments with respect to identification of patients who may benefit from treatment with belantamab is unfair.

Whilst there is currently no predictive biomarker for response to belantamab, the clinical experts present at the appraisal Committee meetings explained that when there is disease response to belantamab, it happens quickly (median time to response is 1.5 months [final analysis, 95% CI: 1.0, 2.1]) and has a long duration. This illustrates that the identification of patients who benefit from belantamab is feasible and can be done rapidly after treatment initiation.

In conclusion, GSK would like to emphasize that the Committee’s decision appears unfair considering the benefit that belantamab may provide to UK patients currently facing a high unmet need for new therapies in the 5L+ TCR MM post-POM setting. GSK would like to express its openness and willingness to discuss alternative positioning(s) in the best interest of UK patients in populations where belantamab could address a substantial unmet need.

## Ground 2 The recommendation is unreasonable in the light of the evidence submitted to NICE

### The Committee’s conclusion in relation to the data from the DREAMM-3 are unreasonable in the light of the evidence submitted.

1. **The DREAMM-3 ITT population is broader than the population considered in the decision problem therefore the committee’s conclusion that it is relevant for this decision problem is unreasonable.**

In section 3.9 of the FDG, the Committee refers to the DREAMM-3 trial conducted in people with RRMM who received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a PI. The Committee recognised that the “ITT population included belantamab being used earlier in the treatment pathway, meaning it is a broader population than that under consideration in this appraisal”. As the DREAMM-3 ITT population does not reflect the licensed indication for belantamab, the patients eligible for treatment, or the decision problem for this appraisal, the conclusion that efficacy data from the ITT population is “relevant” to decision making by the Committee in the current appraisal is unreasonable.

1. **The Committee’s conclusions regarding the DREAMM-3 subgroup data as being the most relevant to this decision problem are unreasonable.**

In response to consultation, GSK submitted data from a very small subgroup of patients from DREAMM-3, defined post hoc, who do reflect the licensed indication for belantamab. The Committee agreed with the evidence assessment group (EAG) that, despite the limitations observed with the subgroup data from the randomised DREAMM-3 trial, this data source was preferable to the non-randomised UK specific evidence presented by the company.

In the draft guidance consultation, clinical experts expressed significant concerns about the rationale behind any statements that the subgroup within the DREAMM-3 trial was proposed as the most reliable dataset. They stated that “*the subgroup represents only about 10% of the total patient population in the study that was designed to define new 3rd line standard of care rather than the 5th line treatment which is the decision problem.*” The clinical experts further explained that “*patients are “selected” rather than truly randomised as the patient populations differ and treatment outcomes in pomalidomide dexamethasone registered have never been reported in any studies of PomDex in the last 10-years.*”

However, there is no indication that the Committee took any of these factors into account or assessed them when considering the weight to be attached to the DREAMM-3 subgroup versus the DREAMM-2 trial and the UK RWE. GSK therefore believes that the Committee’s conclusions regarding the DREAMM-3 subgroup data as being the most relevant to this decision problem are unreasonable.

### The Committee’s failure to recognise belantamab as an innovative intervention with benefits not captured in the economic modelling is inconsistent with the innovation passport granted by MHRA, the evidence submitted by GSK and stakeholders’ comments in response to the consultation on the draft guidance and is therefore unreasonable.

In section 3.21 of the FDG, the Committee considered if belantamab was innovative. The Committee stated that “it did not identify any additional benefits of belantamab not captured in the economic modelling” and therefore concluded “that all additional benefits of belantamab had already been taken into account”. The Committee did not comment explicitly on whether it considered belantamab to be innovative.

1. **Belantamab was granted an innovation passport by MHRA.**

The Committee’s conclusions conflict with the Medicines and Healthcare products Regulatory Agency (MHRA) acceptance of the innovative nature of belantamab through award of an Innovation Passport in May 2022, with the goal of accelerating access for UK patients to novel medicines. No explanation has been provided by the Committee for diverging from MHRA’s assessment and it is GSK’s firm position that belantamab offers substantial benefits to eligible patients, some of which are not captured in the economic analysis.

1. **The innovative nature of belantamab is well recognised by clinicians, patients, and other stakeholders.**

The innovative nature of belantamab is demonstrated by the following:

* Belantamab would be the first BCMA targeted therapy within the NICE pathway, providing a novel approach to treatment of patients at high clinical need.
* There is considerable advocacy and support from the UK multiple myeloma clinical and patient communities highlighting that belantamab is a much-needed medicine and suggesting that more weight should be given to the innovative nature of belantamab, as evidenced in the stakeholder consultations on the draft guidance.
	+ Myeloma UK stated “*The significant unmet need among the patient population relevant to this appraisal and the innovative nature of belantamab should be grounds for a more flexible approach to considering this treatment a candidate for managed access. […] We believe the Committee should give further weight to the innovative nature of this treatment.”*
	+ Clinical experts recognised that “*BCMA targeted therapy is the innovation in myeloma. Across Western countries use of BCMA targeted therapy is standard of care for patients in 5th line. Belantamab mafodotin is the only antibody drug conjugate that can be utilised as 5th line for the multiply pre-treated and comorbid myeloma patient population.*”
1. **The Committee’s conclusions that belantamab does not offer patients additional benefits not captured in the economic evaluation is inconsistent with the evidence submitted in GSK original submission (document B - section B.3.13).**

First, the introduction of a new mechanism of action in the MM treatment paradigm for a population of heavily pre-treated patients would improve patients’ QoL by bringing hope to a group who otherwise are left with poor treatment options which may negatively impact their and their family’s mental health.

Moreover, the burden on caregivers and impact on their QoL is not reflected in the QALY calculations. The limited effective treatment options in this setting may have a detrimental psychological impact on patients, leaving them feeling hopeless. This consideration was also highlighted by Myeloma UK in their response to the draft guidance stating that, “*The approval of this novel therapy would be a welcome step towards building a clinically optimal treatment pathway with the breadth of options and mechanisms of action required to meet the needs of multiply relapsed myeloma patients. This would also offer patients hope that belantamab can serve as a bridge to other innovative treatments coming down the pipeline, which has an immensely positive impact on their psychological well-being.*”

1. **The Committee has itself noted the particular benefits of belantamab but has failed to take these matters into account at section 3.21 of the FDG**

At section 3.1 of the FDG, the Committee notes:

* The fact that belantamab is the only antibody treatment to be licensed for MM that targets the BCMA;
* That belantamab benefits some patients because it is not used with combination steroids which may have toxic side effects;
* The clinical need of patients with triple-class refractory MM after 4 or more treatments;

In summary therefore, while the Committee was provided with material evidence of benefits of belantamab not reflected in the economic modelling, these have been disregarded by the Committee in the context of its consideration of innovation at section 3.21 of the FGD. This is unreasonable.

### The Committee’s conclusions on the severity modifiers in the 5L+ TCR post-POM subgroup are unreasonable given the evidence indicating the applicability of a 1.7 severity weight.

In section 3.17 of the FDG, the Committee, at the second committee meeting, concluded that it had not been presented with compelling evidence to change its initial conclusion that a severity weight of 1.2 applied to the QALYs would likely be appropriate.

1. **The outcomes for PanoBorDex supporting the severity modifier calculations are realistic and plausible.**

Notwithstanding whether the Committee considers PanoBorDex to be an appropriate comparator in the 5L+ TCR post-POM, a 1.7 severity modifier should be applied based on the QALY generated for PanoBorDex in the economic analysis.

In the original submission (document B – section B.1.3.3.1), GSK presented evidence suggesting that efficacy outcomes for PanoBorDex in the 5L+ TCR MM population are likely to be poor.

This evidence confirms that despite the uncertainty resulting from the limited efficacy data available for PanoBorDex in the subpopulation (i.e., 5L+ TCR MM post-POM), the outcomes generated from the CEM model are realistic and plausible and support the 1.7 severity weight. Thus, the Committee decision to apply the 1.2 severity modifier is unreasonable.

1. **The Committee’s conclusion that it had not been presented evidence to support a 1.7 severity weight is unreasonable and fails to consider the evidence presented by GSK’s and the EAG’s.**

Both GSK’s and the EAG’s severity modifier calculations in the 5L+ TCR post-POM population (using the age and male: female ratio from the DREAMM-2 and the NCRAS dataset, respectively) demonstrate that a 1.7 severity modifier is applicable. Hence, GSK request that the Committee reconsider the choice of severity weight based on evidence submitted by GSK and confirmed by the EAG or provide a clear and transparent rationale for deciding otherwise.

1. **The Committee’s decision on severity modifier is procedurally unfair and unreasonable in view of the purpose of the severity modifier described by the NICE methods and in absence of clear guidance on how uncertainty can affect the choice of severity weighting.**

The NICE Manual for health technology evaluations, paragraphs 6.2.12 to 6.2.22 “Decision modifiers: severity” describe the objectives and methods to calculate the modifier that reflect the severity of a condition and potentially the extent of unmet need.

In paragraph 6.2.12, it is stated that “The Committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care). The extent of unmet health need is reflected within the severity definition.”

In section 3.17 of the FDG, the Committee explained that “It [the Committee] considered that any QALY shortfall estimates based on this data [the company’s indirect treatment comparison comparing belantamab with panobinostat plus bortezomib and dexamethasone] were likely to be highly uncertain because the MAIC included a very small number of people on panobinostat plus bortezomib and dexamethasone.” It therefore stated that it “had not been presented with compelling evidence to change its initial conclusion that a severity weighting of 1.2 applied to the QALYs would likely be appropriate.”

As indicated under appeal point 1(a).4, the lack of data for PanoBorDex exerts a material effect in this appraisal including prejudicing the assessment of QALY shortfalls. The NCRAS study provides the only and therefore most robust evidence of the efficacy of PanoBorDex in UK patients with 5L+ TCR MM. When assessing the MAIC adjustments were made only to the belantamab arm meaning that the QALY calculations rely on all the evidence available for PanoBorDex and have not introduced bias. In these circumstances the evidence presented for the QALY shortfall is the most robust possible in patients with 5L+ TCR MM, justifying a severity modifier of 1.7.

GSK therefore considers that the Committee’s decision to select a 1.2 severity modifier is unreasonable in view of the evidence and methods used to calculate the QALY associated with PanoBorDex and the purpose and guidelines for severity modifiers decisions developed by NICE.

# The determination of this appeal

GSK request that this appeal is determined at an oral appeal.

# Requested outcome following appeal

The Appeal Panel is respectfully requested to return this appraisal for further consideration by the Appraisal Committee with the following directions:

* The Committee should reconsider and explain its approach to the UK RWE, including the NPP study, which offers an important and relevant predictor of belantamab efficacy in UK clinical practice.
* The Committee should reconsider the use of belantamab through managed access, in accordance with NICE’s procedures and in circumstances where this would allow for the collection of further UK RWE for belantamab and thus, reduce the uncertainty around long-term benefits and comparative efficacy of belantamab vs PanoBorDex in patients with 5L+ TCR MM post-POM.
* The Committee should allow for adequate consideration and consultation in the context of changes to the treatment pathway following TA897, so that guidance for belantamab is relevant to NHS practice when issued.
* DREAMM-3 should not be used for the purposes of assessment of efficacy in the context of this appraisal.
* Belantamab should be recognised as an innovative treatment with benefits not currently captured in the economic modelling and the Committee should reconsider the assessment of the severity modifiers to be applied.
* The Committee should demonstrate a degree of flexibility in view of the high unmet need and engage in discussions with GSK on whether an alternative positioning could lead to providing patients access to belantamab, a much needed and recognised innovative intervention.

Yours sincerely,

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| **GSK** |
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