Dr Mark Chakravarty

Lead Non-Executive Director for Appeals

National Institute for Health and Care Excellence

2nd Floor

2 Redman Place

London E20 1JQ

25 August 2023

Dear Dr Chakravarty,

**Appeal against the Final Draft Guidance (FDG) for Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more prior therapies [ID2701]**

Thank you for your letter dated 11 August 2023, in which you provide your initial view on the admissibility of the points of appeal set out in GSK’s letter of appeal of 4 August 2023.

We welcome your conclusion that certain of our appeal points may proceed to an oral hearing and, as suggested in your letter, we provide further detail to elaborate or clarify those appeal points that you are currently not minded to refer to the appeal panel.

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

You express the preliminary view that Appeal point 1(a).1 should be considered under Ground 2, rather than Ground 1.

GSK’s appeal under point 1(a).1 was based on two matters. Your preliminary view addresses these separately and we respond to those matters in the same way.

1. The first point made by GSK was that the Committee has not explained its conclusion, at paragraph 3.8 of the FDG, that the UK RWE considered in this evaluation and relied upon for the purposes of GSK’s naïve unadjusted comparison is subject to “potential bias”.

In considering this part of GSK’s appeal, you say that the Committee has provided explanations for its concerns regarding the data from the NPP at paragraph 3.8 of the FDG and on that basis suggest that you do not accept that GSK is "unable to understand the Committee’s reasons for rejecting the naïve comparison". By way of illustration, you list four reasons, which you say were given by the Committee to explain its rejection of the NPP data, including that “the extent and direction of the potential bias was unclear in the company’s naive comparison”.

However, the statements relied upon raised in your letter do not explain why the Committee concluded that the NPP was affected by “potential bias”, even though these data were obtained from use of belantamab in actual clinical practice in the UK. In particular, the fourth extract from the FDG quoted in your letter is, as explained in our appeal letter, the very statement which GSK believes lacks transparency.

For completeness:

* The first statement quoted in your letter simply says that the EAG considered that the feasibility of the MAIC was not improved by using NPP. This was a conclusion by the EAG, and it is unclear whether it was relied upon by the Committee. Even it was relied upon by the Committee this statement does not explain why the Committee concluded that the NPP was potentially affected by bias.
* The second statement quoted in your letter is a further conclusion by the EAG regarding the fact that the NPP was less mature and had a smaller sample size than DREAMM-2. Again, it is unclear whether this point was relied upon by the Committee. If it was relied upon, it is unclear why the Committee concluded that these matters potentially result in bias.
* The third statement quoted in your letter was that median progression-free survival was longer in NPP than in DREAMM-2, which the Committee considered suggested that the population in NPP may be less likely to have disease progression. Again, it is unclear whether the Committee considered any alternative explanations for the more favourable outcomes in NPP – including whether these were accounted for by the fact that the patients receiving treatment represented the patients who would actually be treated in clinical practice.

In summary therefore, the substance of GSK’s appeal is the apparent rejection of real-world evidence, simply because this is different to clinical trial data and therefore assumed to be “biased”, without any valid explanation.

1. The second point made by GSK was that the Committee's conclusion in relation to the NPP is inconsistent with the NICE 2021-2026 strategy.

In considering this point you express the preliminary view that such inconsistency would not be appealable on the basis that it does not appear in the Manual.

However, as recognised in your letter, procedural fairness extends beyond the written scope of the Manual. Clearly any procedural obligation expressly stated in the Manual must be followed but, in addition, NICE and the Appraisal Committee is required to interpret the Manual in accordance with broader standards of procedural fairness as a matter of English administrative law. To the extent that NICE has publicly committed itself to a particular policy (in this case, use of real-world evidence) stakeholders are entitled to expect that such commitment will be reflected in the way in which it approaches appraisals. In this case, the Committee’s refusal to base recommendations on real-world evidence conflicts with NICE’s stated policy and is therefore unfair.

Overall, therefore, while we note your preliminary view that appeal point 1(a).1 should be considered under Ground 2, for the reasons set out above, we would prefer to present our case under Ground 1.

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

Your view that subpoint (A) is admitted is noted.

You express the preliminary view that subpoint (B), which relates to the fact that the Committee’s apparent conclusion that only comparative data could sufficiently support the case for recommendation disregards the benefits of real-world evidence, should be brought under Ground 2. Your reason is simply that, you say, nothing in our appeal letter supports procedural unfairness.

Our appeal letter referred to the reasons given by the Committee at paragraph 3.19 of the FDG for rejecting managed access to belantamab. These reasons were limited to the fact that managed access would not produce data on the efficacy of belantamab relative to comparators. However, this reason disregards other evidence relating to use of belantamab that would be generated through managed access and would address uncertainties identified by the Committee. Paragraph 5.5.25 of NICE’s guide to Health Technology Evaluations: the Manual (the Manual), provides that:

“*A feasibility assessment will be done by NICE to identify if the proposed data collection can produce new evidence to address the significant uncertainties, without undue burden on the NHS. The feasibility assessment process will involve engagement with a range of stakeholders, including the company, clinicians, patients and their representatives, and NHS data custodians. The extent of engagement activities will be proportionate to the complexity of the data collection proposal*”.

The feasibility study should be shared with the Committee, company and stakeholders 28 days before the Committee Meeting. In this case, no feasibility study was provided to GSK and we therefore assume none was conducted. It is therefore clear that no consideration was given to the data that would be generated through use of belantamab under a managed access arrangement and how this would address the uncertainties identified by the Committee, beyond stating that such data would not be comparative.

Failure to take into account relevant factors or relevant evidence is a clear example of procedural unfairness and we therefore maintain that this aspect of GSK’s appeal should be considered under Ground 1.

* 1. **Appeal point 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.**

Your view is noted.

* 1. **Appeal point 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 a less effective treatment with less evidence of benefit**

You express the preliminary view that Appeal point 1(a).4 should not be admitted under Ground 1 because, you suggest, nothing in our appeal letter indicates a departure from the requirements of the Manual or other aspects of procedural fairness. You suggest that you might consider admitting the point under Ground 2, based on our response to your letter.

The issue raised in Appeal point 1(a).4 is the inconsistent approach followed in relation to the assessment of belantamab in 5L+ TCR MM patients who had previously received treatment with pomalidomide as compared with the assessment of PanoBorDex (current standard treatment) in the same patient population. When NICE conducted an appraisal of PanoBorDex (TA380), the recommendation by the Committee covered third and subsequent lines, even though there was no evidence reported in TA380 supporting the efficacy and cost-effectiveness of PanoBorDex as fifth (or subsequent) line treatment. There has been little use of PanoBorDex in the fifth line setting following TA380 and there is accordingly very limited data in the NCRAS database.

The Committee considering belantamab accepted that “efficacy outcomes for panobinostat plus bortezomib and dexamethasone were likely to be poor in this population”. However, in circumstances where the data for PanoBorDex are limited, declined to recommend belantamab due to uncertainties over the comparison of the two therapies.

The result is both unfair and perverse. NICE has recommended PanoBorDex without data but declines to recommend a product that is almost certainly more clinically and cost effective because of lack of evidence for the comparator. This is inconsistent with the general approach to assessment of evidence at paragraph 3.2.1 of the Manual and disregards the requirement for a consistent approach at paragraph 5.1. It biases all appraisals in favour of older therapies just in respect of their being older. The unacceptable outcome should have been taken into account by the Committee and resulted in a more flexible approach to the appraisal of belantamab consistent with the requirements of the Manual.

* 1. **Appeal point 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**

You express the preliminary view that this point of appeal is not valid. Your reason seems to be that, if it is possible to define a subgroup of patients in which belantamab offers significant benefits, it was a matter for GSK to carry out the associated cost effectiveness modelling.

However, this point of appeal is limited to whether, contrary to the Committee’s conclusion, a subgroup can be identified. At paragraph 3.10 of the FDG, the Committee expressed the view that it could not, disregarding the evidence from the clinical experts that when there is a disease response to belantamab this happens quickly. No explanation is provided to justify rejecting the views of the clinical experts, a requirement of transparency heightened in view of the level of clinical need of affected patients.

1. **Ground 2 The recommendation is unreasonable in the light of the evidence submitted to NICE.**
	1. **Appeal point 2.1: The Committee’s conclusion in relation to the data from the DREAMM-3 are unreasonable in the light of the evidence submitted**

You say that you are minded to refer this appeal point to the Appeal Panel limited to the argument under (B) that the Committee’s conclusions regarding the DREAMM-3 subgroup data as being the most relevant to this decision problem are unreasonable.

In relation to part (A), you express the preliminary view that GSK’s case that the Committee’s conclusion at 3.9 of the FDG that "the DREAMM-3 ITT population results were relevant to its decision making" is unarguable because the Committee was aware of the points raised by GSK in its appeal, but nevertheless considered the data from DREAMM-3 to be relevant to decision making.

We respectfully suggest that this is not the correct test for an appeal under Ground 2. GSK understands that the Committee was aware of the points raised in our appeal and it is GSK’s strong view that the assessment of the Committee, which rejected those arguments was unreasonable. In particular, we consider that it is perverse to base conclusions regarding the efficacy of belantamab in fifth line use on a clinical trial which investigated a different indication. This cannot on any view be viewed as an unarguable point and we firmly believe Appeal point 2.1 should proceed to appeal.

* 1. **Appeal point 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.**

You consider each of the matters raised under Appeal point 2.2 and consider each individually. Following that approach you suggest that this point of appeal should not proceed to a hearing.

The four subpoints raised under Appeal point 2.2 should however be considered cumulatively as providing evidence of the innovative nature of belantamab that has not been reflected in the economic modelling. We respond however to the issues you have raised under each of these in turn.

Under (A) you say that you are unpersuaded that the fact of an innovation passport granted by MHRA means that NICE should also conclude that belantamab is innovative. GSK does not however suggest that the assessments by MHRA and NICE are identical, however in circumstances where the innovation passport is a part of the Innovation Licencing and Access Pathway (ILAP), which includes NICE, it is clearly the case that there is a material overlap between the innovation passport and NICE’s assessments. In these circumstances a difference in terms of innovation status between the innovation passport designation and NICE’s independent processes, clearly requires justification if NICE is not to undermine its own conclusions under ILAP.

You say that the issues raised under (B) (the fact that belantamab is the first BCMA targeted treatment) do not identify any benefit that has not already been taken into account in the modelling. However, as the first BCMA targeted treatment, belantamab provides a new approach to therapy for heavily treated multiple myeloma patients. The addition of a further treatment option provides a benefit not currently recognised in the economic modelling, and indeed a benefit for which there does not currently exist an accepted method of incorporating into economic modelling. This therefore heightens the requirement on the Committee to fully incorporate qualitative assessment of innovation into their decision-making.

In relation to (C), you say that it was for GSK to identify such benefits and incorporate them in the modelling. With respect, we disagree. While we accept that ideally all benefits of treatment would be captured in the economic modelling, inevitably there will be effects that are not captured. The purpose of the assessment at paragraph 3.21 of the FDG is to identify whether there are such benefits so that the Committee can form a view about whether its assessment of cost effectiveness is likely to be pessimistic. In circumstances where the Committee believes there is uncertainty surrounding the assessment of cost-effectiveness, a conclusion that there are additional benefits not currently captured may provide reassurance that a recommendation may be made.

You say that GSK should explain how the matters raised under (D) should have been taken into account by the Committee. As explained in our response to (C), these matters are not currently reflected in the economic modelling but represent additional benefits not currently taken into account. As stated under (C), they indicate that any conclusion by the Committee on cost effectiveness is likely to be pessimistic and provide reassurance in the context of the uncertainty identified by the Committee.

Overall, therefore, we believe that belantamab is clearly an innovative product and that important benefits have not been taken into account. The failure of the Committee to consider such matters in the context of paragraph 3.21 of the FDG is therefore unreasonable.

* 1. **Appeal point 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.**

Your view is noted.

We hope that this letter addresses the concerns raised in your letter of 11 August 2023. If any aspect of our appeal remains unclear, we will be pleased to provide further assistance. Alternatively, we look forward to receiving your final scrutiny letter.

Yours sincerely,

**GSK**