Dr Mark Chakravarty

Lead Non-Executive Director for Appeals

National Institute for Health and Care Excellence

2nd Floor

2 Redman Place

London E20 1JQ

17 January 2023

Dear Dr Chakravarty,

**Appeal against the Final Appraisal Document for**  **Daratumumab in combination for the treatment of adult patients with Light-Chain (AL) amyloidosis**

Thank you for your letter dated 22 December 2022, in which you set out your preliminary views in relation to the admissibility of the points of appeal in our letter of appeal dated 16 December 2022.

We now provide, as you suggested in your letter, additional detail to elaborate, comment on or clarify those points of appeal (listed below) where your preliminary view was that these should not be referred to the appeal panel.

**Ground 1**

**Appeal point 1(a).1 The Appraisal Committee has failed to take into account factors other than uncertainty when defining the ICER threshold for this appraisal**

Thank you for confirming that this point of appeal is admissible.

**Appeal point 1(a).2 The Appraisal Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” disregards substantial evidence submitted by Janssen in support of complete haematological response as a surrogate endpoint for overall survival.**

You express the preliminary view that this point of appeal should not be permitted to proceed to an oral hearing on the basis that there is no direct evidence in relation to overall survival (OS) and, you say, the Committee gave detailed consideration to use of complete haematological response as a surrogate endpoint.

However, the focus of this point of appeal is a procedural one. In summary, this is the fact that, despite the consideration given by the Committee to the use of complete haematological response as a surrogate endpoint for OS, the Committee failed to take into account important parts of the evidence. These are listed in our appeal letter and include:

* The absence of any recognition that substantial delay in major organ deterioration (an endpoint evidenced in the data for daratumumab in combination relative to standard care) is an endpoint closely linked to survival, a factor which supports the use of complete haematological response as a surrogate for OS.
* The additional survival results from the ANDROMEDA safety data at a median follow up of 20.3 months were used to update the economic model and submitted in response to the ACD, with the agreement of NICE; these data, while immature, provide directional (direct) evidence of a survival advantage in patients receiving daratumumab in combination (a 6.6% higher survival at 20.3 months median follow-up in patients treated with DBCd as compared with patients on BCd only, point 4 Janssen response to ACD), but this is not recognised in the FAD.

The FAD gives no indication that the evidence listed in Janssen’s appeal letter was taken into account by the Appraisal Committee when reaching its conclusion that it had not been shown that use of daratumumab in combination improves OS and the failure to take into account relevant evidence or to explain why important evidence has not been relied upon (lack of transparency) is a strong marker for procedural unfairness.

In these circumstances, while you say that the Committee gave detailed consideration to the question of whether complete haematological response should be viewed as a surrogate for OS, this is limited to paragraph 3.7 of the FAD and does not answer the point that such consideration was inadequate because it did not take account of important relevant evidence.

Finally and for completeness, when considering appeal point 1(a)(2) you refer to your preliminary views on appeal point 2.2, in which you reference Janssen’s original submission and the ERG’s initial report dated September 2021. However, these documents do not address the procedural point made in this point of appeal:

1. both of the documents referenced in your preliminary consideration of appeal point 2.2 predate certain evidence which was supplied after and in response to the ERG’s initial report. This additional evidence was disregarded by the Committee.
2. Furthermore, in circumstances where the Committee and not the ERG is the decision-maker, the conclusions of the ERG do not determine the ultimate view of the Committee in relation to the evidence relied upon or explain why the Committee seemingly rejected certain evidence submitted by Janssen.

We also refer to our response in relation to appeal point 2.2 below.

## Appeal point 1(a).3 The fact that an expert haematologist was not invited to the first meeting of the Committee was not adequately corrected by inviting such an expert to the second meeting because issues such as the significance of complete haematologic response were not discussed

Thank you for confirming that this point of appeal is admissible.

**Ground 2**

**Appeal point 2.1 The Appraisal Committee’s conclusions that “both ALchemy and EMN23-UK may be representative of UK clinical practice” are unreasonable**

You express the preliminary view that this point of appeal should not be permitted to proceed to an oral hearing on the basis that you say you consider the Committee had sufficient basis to conclude that both ALchemy and EMN23-UK may be representative of UK practice. You refer principally on an extract from the initial ERG report and additionally on the reasoning provided by the Committee at paragraph 3.10 of the FAD.

However, the initial ERG report considered only the EMN23 data rather than EMN23-UK, which was submitted by Janssen in response to the ACD, and the extract quoted in your letter preferring ALchemy is not therefore relevant to the conclusions of the Committee (that *“ALchemy and EMN23-UK may be representative of UK clinical practice”*) as set out in the FAD. Similarly, paragraph 3.10 of the FAD principally considers EMN23 versus ALchemy and only briefly addresses EMN23-UK at the conclusion of the paragraph. This may explain some of the confusion.

Appeal point 2.1 raises the fact that, at paragraph 3.10 of the FAD, the text states “*the clinical experts agreed with the ERG that ALchemy better reflects NHS practice*”, a statement which relates to the experts’ consideration of EMN23 but is factually inaccurate so far as the experts’ comments on EMN23-UK is concerned. The fact that paragraph 3.10 of the FAD includes comments of the experts in relation to EMN23 (the first meeting of the Appraisal Committee) but not EMN23-UK, which formed the basis for discussion at the second Appraisal Committee meeting, is unbalanced and misleading. Importantly, the haematology expert attended only the second meeting of the Appraisal Committee, so the statement quoted at paragraph 3.10 of the FAD cannot reflect their opinion. In fact, when the experts discussed EMN23-UK and ALchemy at the second Committee meeting, they expressed concerns regarding the data from ALchemy including the observation of the haematology expert that the Kaplan Meier curves from ALchemy are implausible. These concerns, which conflict with the statement regarding the position of the experts are not reflected in the FAD, further confirming that the content of paragraph 3.10 is inaccurate and misleading

In addition, the Committee has disregarded the fact, drawn to its attention by Janssen (Point 2, Janssen ACD Response) and also noted by the ERG’s expert, that the haematologic response criteria from ALchemy were not aligned with the response criteria used in ANDROMEDA. Specifically, the ERG’s clinical advisor stated that *“the reclassification of response is important as the older criteria used in the analysis of ALchemy were problematic”* (Page 8, Evidence Review Group’s Critique of the Company’s Response to the ACD).

A further issue with ALchemy was the potential risk of confounding due to treatment switching. This was discussed in the first appraisal committee meeting and referred to in Section 3.11 of the ACD, *“However, in ALCHEMY, response status at 6 months was reported irrespective of previous treatment changes – for instance, a person who switched treatments after 3 months and whose condition subsequently responded would be reported as having a response. This suggests that the response categorisation at 6 months in ANDROMEDA does not match the response categorisation from ALCHEMY.”*

Finally, the fact that patient level data were not available from ALchemy with the result that the inconsistencies identified above could not be corrected, provides a clear reason why EMN23-UK should have been preferred.

In summary therefore, the unbalanced reference to the views of the clinical experts together with the failure to consider the implausible Kaplan Meier curves from ALchemy, the inconsistency between the haematologic response criteria used by ALchemy and in ANDROMEDA and the lack of access to patient level data from ALchemy indicate that the approach of the Committee in concluding that both ALchemy and EMN23-UK may be representative of UK clinical practice, is unreasonable.

## Appeal point 2.2 The Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” conflicts with the balance of the available evidence.

You express the preliminary view that this point of appeal should not be permitted to proceed to an oral hearing on the basis that there was no direct evidence in relation to OS and, while the committee was invited to consider complete haematological response as a surrogate endpoint, “a clear basis for the committee’s concern in respect of overall survival data is apparent from the evidence submitted to it”. As indicated in our response to your preliminary view in relation to appeal point 1(a).2 above, you refer to Janssen’s original submission and the ERG’s initial report dated September 2021.

This point of appeal is based on Janssen’s case that the Committee’s conclusions are unreasonable in light of the evidence submitted. The matters raised in our response to your preliminary views on appeal point 1(a).2 above (a procedural point based on the fact that the Committee seemingly disregarded important relevant evidence when reaching its conclusions) are also relevant to our response to this point of appeal.

In particular, while you refer to evidence as submitted to NICE in September 2021, at the commencement of this appraisal by Janssen and the ERG, as supporting the Committee’s conclusion that “*it had not been shown if daratumumab in combination improves overall survival*”, it is Janssen’s case: (a) that even at that stage the balance of the evidence indicated that daratumumab in combination is associated with benefit in terms of overall survival; and (b) the material to which you refer disregards all evidence submitted to NICE since September 2021, including the updated analyses from ANDROMEDA based on the 12 months landmark analysis of safety data (with median follow up of 20.3 months), provided in response to the ACD, which demonstrate a 6.6% survival advantage at a median follow-up of 20.3 months (12.4 months landmark analysis) in patients treated with daratumumab in combination.

In particular, the Committee has disregarded the implications of the data demonstrating a delay in major organ deterioration (an endpoint closely linked with OS) in patients treated with daratumumab in combination, when considering the evidence for an OS benefit. It has also failed to take account of the additional survival results from the ANDROMEDA safety data, set at a median follow up of 20.3 months and submitted in response to the ACD which provide direct evidence of an improvement in OS in patients on daratumumab in combination.

Taken together the balance of this evidence supports a survival benefit in patients who receive treatment with daratumumab in combination and the Committee’s conclusion to the contrary is unreasonable.

We hope that the matters set out in this letter have clarified our appeal and that you now agree that all points may proceed to a full hearing.

Yours sincerely

xxxxxxxxxxxxxx

Senior Director, Patient Access, Janssen-Cilag Ltd

