Dr Mark Chakravarty

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16 December 2022

Dear Dr Chakravarty,

# Appeal against the Final Appraisal Determination for ID3748 daratumumab in combination for the treatment of adult patients with Light-Chain (AL) amyloidosis

## Executive Summary

Janssen brings this appeal in order to address serious procedural issues arising in this appraisal and to the reasonableness of the Appraisal Committee’s conclusions following its assessment. Daratumumab with bortezomib, cyclophosphamide and dexamethasone (daratumumab in combination) is licensed for the treatment of adult patients with newly diagnosed Light-Chain (AL) amyloidosis. Janssen’s concerns, and the issues raised in this appeal includes the following points:

### Ground 1(a): in making the assessment that preceded the recommendation, NICE has failed to act fairly

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

### 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.

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.

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

### The Appraisal Committee’s conclusions that “both ALchemy and EMN23-UK may be representative of UK clinical practice” are unreasonable.

### 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.

## Introduction

We provide below background information in relation to Light-Chain (AL) amyloidosis and daratumumab in combination in order to assist the Appeal Panel. This summary is not intended to replace the more detailed information provided by Janssen in its original submission for the purposes of this appraisal.

Amyloid Light-Chain (AL) amyloidosis

Amyloid light-chain (AL) amyloidosis is a rare and debilitating condition caused by an abnormality in certain cells found in the bone marrow, called plasma cells. While plasma cells in healthy people produce normal proteins (called ‘light chain proteins’) to help protect the body from infection, patients with AL amyloidosis produce erroneous forms of these proteins which create amyloid deposits when they enter the bloodstream. These proteins aggregate into thread-like strings (amyloid fibrils) that cannot be cleared easily. Over time, amyloid fibrils build up as AL amyloid deposits in tissues and organs. This gradually stops the organs functioning properly, causing debilitating symptoms and ultimately leading to death. The estimated 4 year survival for affected patients is 54% and around a third of patients die within a year of diagnosis.

In AL amyloidosis, the heart and kidneys are the most commonly affected organs, with approximately 50–70% of patients experiencing cardiac involvement, and up to 70% experiencing renal involvement. Other sites that may be affected include the liver, gastrointestinal tract, soft tissue and peripheral nervous system, with most patients experiencing involvement across multiple organs. Accordingly, patients often present with non-specific symptoms such as weight loss, fatigue, weakness, loss of appetite, bruising of ankles and legs, shortness of breath with minimal exertion, numbness, tingling or pain in hands or feet, blood pressure change, dizziness, GI symptoms such as diarrhoea or constipation, pain and/or kidney issues. This non-specificity of symptoms poses a challenge for diagnosis and can result in delays of several months or longer for an initial diagnosis.

As the condition progresses, more severe symptoms develop, which may include heart failure. In addition, patients with kidney involvement may experience malabsorption, albuminuria and nephrotic-range proteinuria which impact the quality of life; if diagnosed late, kidney involvement can lead to end-stage renal failure.

The majority of patients with AL amyloidosis fail to achieve a complete haematologic response (CHR) following standard therapy (e.g. with cyclophosphamide, bortezomib and dexamethasome [BCd]), and eventually, almost all patients experience haematologic relapse and progression of organ involvement, and ultimately death. Prior to authorisation of daratumumab in combination, there was no licenced treatment for AL amyloidosis available in the UK.

According to the National Amyloidosis Centre, the incidence of amyloidosis in the UK is 1 in 100,000 each year, of which 60% are AL amyloidosis patients, this is around 266 patients each year. Acknowledging the rarity and severity of the disease and the absence of authorised medicines for the treatment of this condition, daratumumab in combination was granted orphan designation by both the European Medicines Agency (EMA) and the MHRA for the treatment of AL amyloidosis.

Daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone

Daratumumab in combination with BCd was granted a marketing authorisation by the European Commission under the EU centralised procedure on 21 June 2021, and by the MHRA in the UK on 13 October 2021, for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

The efficacy and safety of daratumumab in combination has been compared directly to BCd in ANDROMEDA, a pivotal, Phase III randomised controlled trial of newly diagnosed AL amyloidosis patients. Within ANDROMEDA, daratumumab in combination has demonstrated a rapid and deep haematologic response, as well as high rates of cardiac and renal response, relative to BCd. The introduction of daratumumab in combination would fulfil a significant unmet need for a group of patients who suffer from a dearth of effective and tolerable treatment options and face an extremely limited prognosis and life expectancy.

In the ANDROMEDA study, patients with Stage IIIb cardiac disease were excluded during the screening period from participating in the trial, as they are not typically candidates for BCd at the specific dose and dosing schedule used in the trial. However, clinical expert opinion supports that patients would be treated with daratumumab in combination in clinical practice should daratumumab in combination be recommended for use in the UK, as this would fulfil a significant unmet need in these patients.

**Procedural History of the Appraisal**

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| **Date** | **Event** |
| 15 July 2020 –  12 August 2020 | Consultation on suggested remit, draft scope and provisional stakeholder list of consultees and commentators |
| 14 September 2020 | Scoping workshop |
| 20 November 2020 | Referral to NICE (following on from a request from the company, the timelines for this appraisal was revised and the appraisal began in mid-Apr 2021) |
| 20 April 2021 | Invitation to participate |
| 20 April 2021 | Final scope |
| 21 June 2021 | European Commission grants marketing authorisation for daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed AL amyloidosis |
| 23 June 2021 | Janssen submission to NICE |
| 26 August 2021 | Evidence Review Group Report prepared by University of York |
| 13 October 2021 | MHRA grants marketing authorisation for daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed AL amyloidosis in the UK |
| 8 December 2021 | First appraisal committee meeting |
| 20 January 2022 –  10 February 2022 | Appraisal Consultation Document |
| 7 February 2022 | Closing date for comments from non-company consultees and commentators |
| 9 March 2022 | Janssen requested a delay to the second committee meeting to allow time to collect more information to address concern highlighted in the appraisal consultation document |
| 15 July 2022 | Janssen’s response to appraisal committee decision |
| 13 October 2022 | Second appraisal committee meeting |
| 2 December 2022 | Final Appraisal Document |

**Grounds of Appeal**

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

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

At paragraph 3.20 of the Final Appraisal Document, the Committee sets out its conclusions regarding the ICER threshold that should apply to this appraisal. The heading to paragraph 3.20 states:

*“The uncertainty means an acceptable ICER is £20,000 per QALY gained”*

Paragraph 3.20 then refers to areas of uncertainty in the evidence and the modelling and concludes:

*“The committee concluded that because of the high uncertainty in the modelling, that an acceptable ICER would be well below £30,000 per QALY gained”*

However, while Janssen recognises that NICE’s procedures provide that the Committee will be more cautious about recommending a treatment where there is uncertainty, in defining an ICER threshold the Committee is required to take into account factors additional to uncertainty, including:

The rarity of the disease under consideration:

“However, the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases” (paragraph 6.2.16 of NICE’s Methods Guide)

Whether there are benefits of treatment not adequately captured in the QALY:

“The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure” (paragraph 6.3.3 of NICE’s Methods Guide).

The degree of clinical need of persons eligible for treatment with daratumumab in combination:

Section 233 of the Health and Social Care Act 2012 requires NICE, in exercising its functions to have regard to the degree of need of persons in England for health.

The indication under consideration in this appraisal is an ultra-orphan one with an estimated 233 patients each year eligible for treatment with daratumumab in combination, as explained above. The rarity of the disease means that there are few patients to participate in clinical trials and some uncertainty in relation to the evidence is inevitable. These challenges in investigating very rare diseases are recognised in NICE’s Highly Specialised Technology evaluation programme, to which daratumumab in combination would have been routed, had it not been for other indications for use of daratumumab. The existence of other indications does not however mean that it is easier to eliminate uncertainty when investigating daratumumab in combination for AL amyloidosis and, if the Committee fails to recognise this in its consideration of such treatments then this acts as a major barrier to patient access to treatments for rare diseases. However, the FAD gives no indication that the rarity of AL amyloidosis was taken into account by the Committee in the context of the uncertainties referenced at paragraph 3.20 of the FAD and the resulting conclusion in relation to the appropriate ICER threshold.

The Committee acknowledge at paragraph 3.19 of the FAD that

“*there may be benefits with daratumumab in combination that were not fully captured in the modelling, such as benefits for people with concomitant multiple myeloma. The committee concluded that daratumumab in combination is innovative and would take this into consideration in its decision making*.”

In addition to benefits highlighted as not fully captured in paragraph 3.19 of the FAD, Janssen in response to the ACD, highlighted a further benefit that is not fully captured. This benefit was highlighted by the ERG during the first ACM and is the survival benefit expected to accrue from deeper / more sustained response associated with daratumumab maintenance therapy that is not captured in the economic model. As part of the response to ACD (point 4) Janssen submitted additional analyses using ANDROMEDA data demonstrating that:

Following treatment with daratumumab in combination a higher proportion of patients versus BCd, at 3 months and 6 months sustained their response between cycles 7 to 24 highlighting that continuous use of daratumumab is associated with higher levels of sustained response (response to ACD, point 4 and Appendix 3, Table 16)

Results of safety data at a median follow up of 20.3 months demonstrate that the observed ratio of surviving patients is 6.6% higher in patients treated with daratumumab in combination compared with patients on BCd only (response to ACD, point 4, Table 2)

The Committee, in paragraph 3.14 of the FAD did not accept the company’s approach to modelling this but accepted that

*“modelling an expected survival benefit for daratumumab maintenance treatment may be reasonable in principle”*

Overall, paragraph 3.20 of the FAD provides no indication that the innovative nature of daratumumab in combination and benefits not fully captured in the modelling were taken into account when determining the appropriate ICER threshold in accordance with paragraph 6.3.3 of NICE’s Methods Guide.

In terms of clinical need, persons eligible for treatment with daratumumab in combination score very highly. AL amyloidosis is a serious condition and, as recognised by the Committee, patients with severe or advanced disease have a particularly poor prognosis. At paragraph 3.18 the FAD states:

*“The committee recalled earlier comments from the clinical experts that people with cardiac or renal failure had more severe disease, and that if the condition causes heart failure (cardiac stage 3b disease), the median survival is about 4.5 months”*

The severity of disease for these patients, who form a clinically distinct group, is demonstrated by the fact that they would satisfy the criteria for application of the end of life criteria, if considered separately from the full population of patients eligible for treatment, in accordance with the daratumumab marketing authorisation.

Daratumumab in combination addresses this clinical need. It offers substanstial benefits to affected patients, including the most severely affected, in circumstances where there is currently no licensed treatment available in the UK. The results of subgroup analyses stratifying ANDROMEDA data by cardiac disease stage, (Key Issue 1, Technical Engagement Response document) demonstrates that the relative treatment effect of daratumumab in combination consecutively increases with increasing severity of cardiac disease versus BCd, where the opposite is observed. Therefore, the adopted assumption that the relative treatment benefit of daratumumab in combination versus BCd observed in ANDROMEDA trial is generalisable to patients with advanced cardiac disease (stage IIIb) is conservative.

However, despite recognising the high level of clinical need of affected patients and the lack of licenced treatment alternatives, there is no indication that this was taken into account by the Committee in considering the applicable ICER threshold.

In summary therefore, the Committee appears to have based its decision on the appropriate ICER threshold exclusively on uncertainty issues, disregarding the obligation in the Methods Guide to consider factors including the rarity of the disease under consideration, benefits not fully captured in the QALY calculation/ modelling and the high level of clinical need of patients with AL amyloidosis.

If contrary to the wording in the FAD, the Committee has taken into account such matters, such assessment lacks transparency, cannot be understood or tested and is therefore procedurally unfair.

**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.

At paragraph 3.7 of the FAD the Committee concludes that

*“it had not been shown if daratumumab in combination improves overall survival”*

This statement fails to take into consideration the evidence submitted by Janssen:

* That the primary and meaningful therapeutic goal in the treatment of AL amyloidosis is to achieve a rapid, deep and durable complete haematologic response (Section B.1.3.2 of company submission)
* That complete haematologic response is a clinically meaningful outcome, demonstrated by multiple studies establishing a relationship between deeper haematologic response and improved prognosis for AL amyloidosis patients, with each successive category of response achieved associated with delayed disease progression, improved organ response rates and overall survival (Section B.2.6.1 of company submission)
* The evidence from ANDROMEDA on the early, profound and durable complete haematologic response seen with daratumumab in combination at 11.4 months median follow-up and 20.3 months median follow-up respectively, where it is also shown that complete haematological response was superior in the daratumumab in combination arm versus BCd (Section B.2.6.1 of company submission)
* That benefits in terms of Major Organ Deterioration (MOD)-PFS, a composite endpoint of multiple clinically observable endpoints, defined as the time from patient randomisation to one of the following events (whichever comes first):
* death
* cardiac deterioration (require cardiac transplant, left ventricular assist device, or intra-aortic balloon pump)
* end stage renal disease requiring haemodialysis or renal transplant, or
* haematologic progression per consensus guidelines

are all closely linked to OS

* that disease progression in AL amyloidosis is evaluated according to a range of different biomarkers in clinical practice (because of the heterogeneity in presentation of disease). Due to the complexity in defining PFS in AL amyloidosis, ANDROMEDA collected MOD-PFS (approved by the FDA and EMA) as a clinically relevant measure of both disease and the benefits of anti-plasma cell therapy (Section B.2.6.2 of company submission)
* That results of MOD-PFS in ANDROMEDA were robust and consistent, favouring daratumumab in combination and demonstrating a substantial delay in haematologic progression, major organ deterioration, or death (Section B.2.6.2 of company submission).
* That clinical experts have explained that delaying or preventing MOD-PFS are important outcomes, as the development of end-stage organ failure is likely to have substantial negative impacts on patient quality of life, with an increasing burden of severe disease symptoms, increased frequency of hospital visits and the continuation of poorly tolerated chemotherapy treatments (Section B.2.6.2 of company submission). Further, progression of AL amyloidosis to end-stage organ failure results in an increased burden to the NHS, such as the significant costs of dialysis to manage end-stage renal failure
* That median OS has not been reached in ANDROMEDA at the time of IA1 data cut-off, therefore all cost-effectiveness results were supported with evidence from high quality real-world evidence specific to the UK supporting the modelled extrapolation of overall survival
* That additional interim survival results were submitted from the ANDROMEDA safety data set at a median follow up of 20.3 months (Janssen response to ACD, point 4, Table 2) demonstrating an increased survival benefit of daratumumab in combination. The observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months was calculated to be 1.066, indicating a 6.6% higher survival in patients treated with daratumumab in combination as compared with patients on BCd only (Janssen response to ACD, point 4, Table 2)

To the extent that the Committee has in fact taken into account these matters, its conclusions are unreasonable (see point 2.2 below)

1a.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

The Committee’s lack of understanding of ‘complete haematologic response’ as the ‘primary’ goal of treatment and its association with improved quality of life and *prolonged* survival is, Janssen considers, a direct result of the fact that no expert haematologist was invited to advise the Committee at the first Committee Meeting on important key issues such as (slide 3, Committee slides for 1st ACM):

* is haematological response clinically meaningful?
* ANDROMEDA trial shows no benefit on overall survival; is modelling haematological response as a surrogate for survival appropriate?

In the absence of such an expert, the Committee was not in a position to fully ascertain the importance of ‘complete haematologic response’ as the ‘primary’ goal of treatment and its association with improved quality of life and *prolonged* survival, not least as, haematologic response represents a key goal in medical society guidelines, and it has been established as a key and independent prognostic factor for survival (independently of baseline patient characteristics such as cardiac involvement).

While the importance of expert haematology advice was recognised before the second meeting of the Appraisal Committee, the attendance of such an expert at that meeting was not adequate to correct the lack of fairness resulting from the lack of expert advice at the first meeting because the Committee did not reconsider the importance and quality of response that is directly associated with improved survival and that patients who attain a complete haematological response have the best overall survival as during the second ACM no discussion took place around whether, in the absence of survival benefit from ANDROMEDA, modelling of haematological response as a surrogate for survival was appropriate.

We consider that the absence of expert haematology advice at the first meeting also impacted:

* The inappropriate concern of the committee in relation to potential confounding issues between CHR and overall survival, even though (a) Janssen provided the ERG with statistical results, that even though have not converged due to the low number of death events in the ANDROMEDA trial, showed no signs of a confounding issue; and (b) available literature on the independent nature of CHR as a surrogate for overall survival
* The Committee’s failure to recognise the implications of results from ALchemy showing lack or no differentiated survival benefits, particularly at the 3 months, between complete responders (CR) and very good partial responders -VGPR

Neither of these two issues were discussed in detail at the second Committee meeting when an expert haematologist was present.

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

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

In paragraph 3.10 the FAD states that *‘the clinical experts agreed with the ERG that ALchemy better reflects NHS practice”*. This sentence fails to fairly reflect first committee meeting discussion, clinical expert input provided during the second committee meeting and evidence submitted in Janssen’s ACD response.

During the first committee meeting, a discussion took place around the inconsistency in categorisation of response at six months between ALchemy and ANDROMEDA. This was followed-up with a statement by the committee in the ACD to “explore a scenario using 6 months, adjusting analyses to ensure consistency in response categorisation between the 2 data sources, ANDROMEDA and ALchemy” (Section 3.21, page 22 of ACD). In our response to ACD, we have confirmed that the approach to the response categorisation of patients who had switched treatments in ALchemy was not aligned to ANDROMEDA, and that Janssen was unable to access patient-level data from ALchemy to be able to undertake the re-categorisation of the response required to correct this issue. And therefore proposed a pragmatic approach using the alternative EMN23- UK cohort.

An additional key issue with the ALchemy data was flagged by the haematologist clinical expert invited to the second appraisal committee meeting. After observing the Kaplan Meier (KM) curves that have compared EMN23-UK study results of survival per level of response, with ALchemy (slide 22 of the committee slides), the clinical expert expressed that “CR patients ‘*do better’* than patients achieving any other response category” when referring to the results shown from ALchemy, where there is no clear separation between CR and VGPR curves for overall survival at the 3 months timepoint. Additionally, in the second ACM the haematologist clinical expert also expressed that extrapolations based on EMN23-UK study results best match their expectation of outcomes in clinical practice.

Janssen’s response to ACD (Point 2) demonstrated that haematologic response criteria from ALchemy was older and therefore not aligned with the response criteria used in the ANDROMEDA study. This is also acknowledged in the ERG’s critique of the company’s response to ACD report, that makes reference to the opinion of their clinical expert when commenting on the reclassification of response criteria implemented by Janssen:

“the *ERG’s clinical advisor indicated that the reclassification of response is important as the older criteria used in the analysis of ALchemy were problematic*” (section 2.2, page 8, ERG’s critique of the company’s response to ACD)

Janssen has also referenced the unavailability to access patient-level data from ALchemy, which would have permitted a re-categorisation of the data, such as that implemented in the EMN23-UK study, and allowed the use of ALchemy data in the cost-effectiveness model, instead of the EMN23-UK data. These factors mean that use of ALchemy data was inappropriate to inform economic modelling and that EMN23-UK data should be used.

In light of the above, Janssen adjusted the UK cohort from the EMN23 study, that has an overlap of ~95% with the population in ALchemy, creating the most robust source of UK-specific real-world evidence to inform the economic model.

Therefore, the conclusion in the FAD in paragraph 3.10 that *“both ALchemy and EMN23-UK may be representative of UK clinical practice”* is unreasonable because it fails to account for first committee meeting discussion, clinical expert input provided during the second committee meeting and evidence submitted in Janssen’s ACD response.

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.

At paragraph 3.7, the Committee concludes (see appeal point 1a.3 above):

“it had not been shown if daratumumab in combination improves overall survival”

However, as explained under appeal point 1a.4 above (which is referenced here), the balance of the available evidence supports a conclusion that daratumumab in combination increases overall survival and the conclusion of the Committee to the contrary is therefore unreasonable.

**THE DETERMINATION OF THIS APPEAL**

Janssen request that this appeal should be determined at an oral hearing.

**REQUESTED OUTCOME FOLLOWING APPEAL**

Janssen respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:

* The Committee to take into account broader considerations in their assessment of an acceptable incremental cost-effectiveness ratio in consideration of the innovative nature of daratumumab in combination, benefits not fully captured in the modelling and the high level of clinical need of patients with AL amyloidosis.
* The Committee to take into account the breadth of evidence submitted regarding the association between CHR and survival outcomes, alongside more recent survival results from ANDROMEDA at a median follow-up of 20.3 months, included as part of the daratumumab maintenance assessment, where it has been shown a 6.6% higher survival benefit in patients treated with daratumumab in combination as compared with patients on BCd
* The Committee to fully address the inclusion of perspectives of expert haematologist with respect to haematological response and its use as a surrogate measure for overall survival
* The Committee to reconsider their assessment of the ALchemy dataset as a plausible data to be included in the economic model.
* The Committee to reconsider their assessment that daratumumab in combination has not demonstrated an overall survival benefit.

Your sincerely

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Senior Director, Patient Access, Janssen-Cilag Ltd