NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

# Advice on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID4067]: Decision of the panel.

## Introduction

1. An appeal panel was convened on 23 September 2024 to consider an appeal against NICE’s final draft guidance (FDG), to the NHS, on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID4067].
2. The appeal panel consisted of:

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| * Professor Jon Cohen | Chair |
| * Dr Biba Stanton | Health service representative |
| * Dr Paul Robinson | Industry representative |
| * Dr Malcolm Oswald | Lay representative |
| * Alina Lourie | Non-executive director of NICE |

1. None of the members of the appeal panel had any competing interest to declare.
2. The panel considered appeals submitted by Sanofi, and Myeloma UK and the UK Myeloma Society.
3. Sanofi was represented by:

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| * Anju Bhalla | Franchise Head Oncology, UK and Ireland |
| * Mersha Chetty | Senior Health Outcomes Manager |
| * Sheetal Fermahan | Senior Scientific Adviser |
| * Adela Williams | Legal Representative |

1. Myeloma UK and the UK Myeloma Society were represented by:

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| * Sarah Love | Legal representative |
| * Nigel Spencer | Myeloma patient |
| * Dr Ceri Bygrave | Consultant Haematologist and Chair of the UK Myeloma Society |
| * Caroline Donoghue | Senior policy officer, Myeloma UK |
| * Dr Neil Rabin | Consultant haematologist |

1. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

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| * Dr Charles Crawley | Chair, Technology Appraisal Committee B |
| * Richard Diaz | Associate Director, NICE |
| * Helen Knight | Director of Medicines Evaluation, NICE |
| * Ross Wilkinson | HTA Analyst, NICE |
| * Dr Daniel Gallacher | Member, Technology Appraisal Committee B |

1. The appeal panel’s legal adviser, Amy Smith, Senior Associate (DAC Beachcroft LLP), was also present.
2. The following members of the appeal panel for technology appraisals and highly specialised technologies were present as silent observers throughout the hearing and panel discussions.

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| * Dr Nurulamin Noor | Health service representative |
| * Dr Stephen Hoole | Health service representative |

1. Under NICE’s appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.
2. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

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

1. Sharmila Nebhrajani OBE, Non-Executive Director and Chairman of NICE, in preliminary correspondence had confirmed that:

* Sanofi had potentially valid grounds of appeal as follows: Grounds 1(a) and 2.
* Myeloma UK and the UK Myeloma Society had potentially valid grounds of appeal as follows: Grounds 1(a) and 2.

1. The evaluation that is the subject of the current appeal provided advice to the NHS on isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma.
2. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Nigel Spencer and Dr Ceri Bygrave, on behalf of the Myeloma UK and UK Myeloma Society , Anju Bhalla, on behalf of Sanofi, and Dr Charles Crawley, on behalf of NICE.

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

### Sanofi Appeal point 1a.1: There is no indication that the Appraisal Committee understood that applying NICE’s standard methodology means that isatuximab cannot be cost effective even at zero price

1. Adela Williams, for Sanofi, stated that this evaluation raises particular complexities because Sanofi's assessment indicated that, despite favourable results for isatuximab with pomalidomide and dexamethasone at fourth line, if NICE's standard methods were applied and the committee's assumptions incorporated then isatuximab with pomalidomide and dexamethasone is not cost effective at zero price. This appeal point is about whether the committee accepted that as a factual matter; the final draft guidance (FDG) reports Sanofi's concerns but does not state whether the committee agreed. Nor does it state the committee's reasons (if it disagreed) or any explanation for how this was taken into account in decision making (if it agreed). Sanofi consider this was clearly a key element in the evaluation, particularly given isatuximab with pomalidomide and dexamethasone demonstrated important benefits, meaning that the committee's conclusions must be explained clearly. Therefore giving no indication in the FDG that this crucial point was understood by committee amounted to a lack of transparency.
2. Dr Charles Crawley, for NICE, stated that this was raised in Sanofi’s submission and noted in the External Assessment Group’s (EAG) report, that the committee had recognised the position and discussed using the non-reference case analysis in detail in both the first and second appraisal committee meetings (ACM1 and ACM2), and that he hoped this was reflected properly in the FDG. Dr Crawley stated that it is implicit from paragraph 3.17 of the FDG that the committee was aware that isatuximab with pomalidomide and dexamethasone would not be cost effective at zero price using standard methods, particularly if using current pomalidomide costs; scenarios using potential generic pomalidomide prices and discounts were explored, including some with isatuximab discounts, and there were some scenarios where isatuximab with pomalidomide and dexamethasone was cost effective without isatuximab being priced at zero, but the committee acknowledged these scenarios were unlikely to be commercially viable.
3. Dr Charles Crawley stated that having recognised the challenge, the committee considered whether this provided a basis for using the non-reference case analysis from Sanofi. Dr Crawley stated that NICE's methods as set out in its current Manual (the Manual) permits the committee to consider (not adopt) non-reference case analyses as part of the decision-making process, alongside reference case analysis, and the committee very much did so. However, the main justification for adopting the non-reference case would have been to remove the background pomalidomide costs and the committee felt unable to do so in this evaluation (for the reasons set out in the discussion of Sanofi's point 1a.6 below). Dr Crawley added that paragraph 3.17 of the FDG is devoted to explaining the committee's consideration of the non-reference case and lists the scenarios proposed by Sanofi. In response to the particular challenges, the committee did consider those scenarios. It also considered use of potential future prices for pomalidomide. It used the non-reference case to agree to accept an Incremental Cost Effectiveness Ratio (ICER) at the top of the range, applying a 1.2 severity modifier so that the ICER threshold in this evaluation was around £34,000 per Quality Adjusted Life Year (QALY).
4. Adela Williams stated that the FDG and committee slides only report Sanofi's position and do not, as is usually the case, state whether the committee agree or accept this. Nor does the FDG explain how the committee took into account this issue. Sanofi consider this a major defect in transparency that makes it difficult to understand the tenor of the guidance. Indeed, the reader could think that the committee's negative recommendation reflects decisions of Sanofi.
5. Dr Charles Crawley stated that the FDG does report that the committee considered the non-reference case analysis removing the pomalidomide and dexamethasone costs and that it considered that analysis but concluded it could not adopt it. A significant part of the discussion in this evaluation was about whether the committee could find a basis for accepting the non-reference case, but the committee could not find a case for doing so.
6. Helen Knight, for NICE, reiterated that the committee looked at the non-reference case, as permitted by 4.4.16 of NICE's Manual, because of the challenge of isatuximab not being cost effective at zero price. It felt it had done what was required under 4.4.16.
7. Adela Williams stated that considering the non-reference case is not a complete answer to how the committee handled the particular challenge of this evaluation because there are other circumstances in which non-reference case analysis is considered.
8. The appeal panel concluded as follows. At the hearing, it was clear that the committee had understood throughout the evaluation process that applying NICE's standard methodology meant that isatuximab with pomalidomide and dexamethasone may not be cost-effective even at zero price. The appellants and the committee agreed that this was not stated explicitly in the FDG (although the committee had considered that it was made implicit by their consideration of the non-reference case analyses). Paragraph 3.17 of the FDG notes Sanofi’s view that isatuximab with pomalidomide and dexamethasone was unlikely to be cost-effective even if offered for free but the appeal panel agreed that the FDG does not explicitly state whether this view was accepted by the committee. The appeal panel is aware that the purpose of the FDG is to summarise the key issues to explain how the committee reached its conclusions (Manual section 6.1.9) but that the FDG cannot be exhaustive. However, the panel judged that this issue was of central importance to decision-making in this evaluation (as discussed under Sanofi's appeal points 1a.2 and 1a.3 and Myeloma UK and the UK Myeloma Society’s point 1a.2, reported below). Procedural fairness requires that the FDG allows a reader to understand the key considerations in reaching a decision. Therefore, the panel judged that procedural fairness required a clear statement in the FDG of the committee’s own view on this point, alongside how it had approached addressing this challenge.
9. The panel therefore upheld the appeal on this point.
10. The panel noted it would expect NICE to consider rewording the FDG to explicitly state the committee’s view on this point, alongside how this affected their decision-making

### Sanofi Appeal point 1a.2: NICE and the Appraisal Committee have not explained how, if at all, they have taken into account the fact that elements of the combination and comparators were appraised under NICE’s previous methodology, subject to a higher ICER threshold.

### Sanofi Appeal point 1a.3: NICE’s proposed discontinuation of the appraisal rather than consideration of a flexible approach to its standard methodology was unfair.

1. Sanofi's points 1a.2 and 1a.3 were discussed together, along with Myeloma UK and the UK Myeloma Society’s point 1a.2. The discussion is reported together below.
2. With regard to Myeloma UK and the UK Myeloma Society’s appeal point 1a.2, Caroline Donoghue, for Myeloma UK and the UK Myeloma Society, stated that structural changes made it impossible for isatuximab with pomalidomide and dexamethasone to be cost effective. The goalposts to achieve cost effectiveness changed, but the disproportionate effect and the issue at the heart of this appeal point came from the fact that isatuximab with pomalidomide and dexamethasone is a combination treatment where the key combination drug pomalidomide had been assessed as cost effective by NICE under NICE's old methods (which applied a higher cost effectiveness threshold) and was unlikely to be so under NICE's new methods. At the time NICE changed its methods, isatuximab with pomalidomide and dexamethasone was the only combination of 3 drugs in the Cancer Drugs Fund (CDF) whose backbone treatment was already recommended under the previous higher threshold. NICE has updated its methods over the years but at no point had Myeloma UK and the UK Myeloma Society seen a methods change have such a significant, unique and disproportionate impact on any evaluation.
3. Sarah Love, for Myeloma UK and the UK Myeloma Society, stated that the question is what fairness required in these unique circumstances. This is context specific, but comes down to whether anyone affected by the change had a fair crack of the whip. Sarah Love stated that in this evaluation the outcome was predetermined due to the unique circumstances, so Myeloma UK and the UK Myeloma Society cannot see how this is fair. Sarah Love stated Myeloma UK and the UK Myeloma Society are not specific about what adjustments should have been made. Sarah Love stated that NICE is a statutory body with discretionary decision-making power and that it may have a policy, and indeed it is a virtue to apply that consistently, but it must be prepared to listen to representations and to depart from its policy in exceptional circumstances. This evaluation is the epitome of that exception. Myeloma UK and the UK Myeloma Society know of no other topic affected in this way. Sarah Love stated that NICE recognises that the comparison in this evaluation may not be fair, and its answer seems to be that it must nevertheless proceed on this flawed basis. This is a refusal to make an exception. Myeloma UK and the UK Myeloma Society accept it may become apparent that a drug would not be cost effective at zero price by the end of an evaluation, and that alone is not unfair, but the problem here was that isatuximab with pomalidomide and dexamethasone could not be cost effective and had no chance from the start due to the unique circumstances.
4. Helen Knight, for NICE, stated that NICE was clear in its methods review about the proposed change from using an end-of-life weighting to a severity modifier, why that was justified and how NICE would implement the change. Helen Knight said that was clearly laid out in the methods review and in the managed access agreement (MAA) with Sanofi when isatuximab with pomalidomide and dexamethasone went into the CDF. NICE has to carry out exit appraisals taking into account the NHS as it is at the time of the evaluation. NICE understands that isatuximab with pomalidomide and dexamethasone is a combination product, but it has to assess the full impact and cost effectiveness of this combination treatment versus standard practice at the point of the evaluation. NICE does not look only at comparators that are cost effective. NICE does not know if the comparators in this case would have been cost effective if assessed under NICE's new methods as it has not done that assessment, and indeed the committee evaluating isatuximab with pomalidomide and dexamethasone could not do that; NICE can only evaluate the intervention, not its comparators. That remains the case whether or not the comparators are a part of a combination.
5. Helen Knight stated that notwithstanding the above, NICE understood there was a challenge; it knew that when isatuximab with pomalidomide and dexamethasone went into the CDF that it may not be cost effective even at zero price and exercised some flexibility at entry to the CDF. It did not know at the point that isatuximab entered the CDF that isatuximab with pomalidomide and dexamethasone could not be cost effective on exit from the CDF as this depended on the updated data, but when the evidence came in NICE could see the potential challenge. That was not a reason not to carry out the evaluation. NICE often evaluates drugs that are not cost effective, and its Manual allows it to stop an evaluation if it is considered futile. It did not do so here. NICE's role is to make up to date evidence-based decisions on what is value for the NHS. When looking at cost effective estimates it was willing to be flexible but the cost effectiveness estimates were significantly above the usual £30,000 ICER threshold. The magnitude of the adjustments to usual process that would have been needed to reach a positive recommendation for isatuximab with pomalidomide and dexamethasone was too significant.
6. Dr Charles Crawley, for NICE, stated that NICE does not know if pomalidomide and dexamethasone would have been cost effective if it had been evaluated under NICE's current Manual. It may have been if a 1.7 severity modifier applied or owing to the comparators available on the NHS at that time.
7. Helen Knight stated that NICE defines comparators by established clinical practice. It is not unusual for a comparator to be not cost effective, and if a comparator is not or is no longer cost effective that is not a reason not to use it as comparator. Comparators are not required to have NICE guidance; whether they do or do not, NICE's methods apply equally. A committee cannot consider the cost effectiveness of comparators. Helen Knight agreed that the circumstances of this evaluation were singular and particular, because isatuximab entered into the CDF following an evaluation under NICE's previous methods and that this may be the only CDF treatment impacted by NICE's change of methods. Helen Knight stated that the recommendation on entry was not, however, for routine commissioning but rather for managed access, that the evidence base had changed and that the issue of isatuximab with pomalidomide and dexamethasone not being cost effective even at zero price could still have been relevant under the old methods.
8. Dr Charles Crawley stated that almost all evaluations have unique elements. There were some aspects of this one that were very challenging. Potentially non-cost effective comparators are not unheard of, and a treatment being not cost effective at zero price has been considered by NICE before and discussed in a 2014 NICE Decision Support Unit (DSU) paper. However, the sequence of issues that came up in this evaluation were different from others.
9. Sarah Love stated that at some point it became clear that isatuximab with pomalidomide and dexamethasone was not cost effective even at zero price. The unique feature of this evaluation was a structural, arithmetic barrier that arose from the singular, unique situation. Sarah Love stated NICE had explained reasons to have a policy but these did not grapple with whether the policy allows exceptions and, if it does, why this was not used in this evaluation. Myeloma UK and the UK Myeloma Society consider it remarkable and perverse, particularly due to need for multiplicity of treatment options, for NICE to have carried out an evaluation with only one outcome on the basis that NICE must take the NHS as it finds it.
10. Caroline Donoghue stated that neither the need for treatment nor the effectiveness of isatuximab with pomalidomide and dexamethasone has changed over time. Thousands of patients are benefitting from isatuximab with pomalidomide and dexamethasone as standard of care at fourth line.
11. Helen Knight, when asked to what extent NICE felt constrained by its processes or felt able to exercise discretion as the previous committee did in TA509, stated that committees must work through the unique circumstances of a topic and that this committee was willing to be flexible and considered and weighed all the evidence. When it looked at cost effectiveness, after considering everything including the non-reference case, the estimates were so significantly above threshold that any flexibility would have been too much. In other cases, such as TA509, the magnitude of the flexibility was acceptable for the committee. But here the magnitude of flexibility was too much given the committee's remit is to evaluate cost effectiveness.
12. Dr Charles Crawley stated the committee was aware of TA509 and that the committee in that appraisal applied the end-of-life modifier (that was available under NICE's old methods, which applied to TA509) when the end-of-life criteria were not formally met. The basis for that recommendation was a very significant prolongation of survival. The problem the committee had in this evaluation was firstly that the end of life criteria were not formally in play (as they are not part of NICE's current methods so the committee would have had to go back to previous methods) and secondly that it was questionable whether the end-of-life criteria would have been met in any event. The committee looked at applying a 1.7 modifier (which has the same effect as the end-of-life modifier) and found that this would not have enabled it to make a positive recommendation. So, even if the committee had applied those changes, which it probably was not able to, that would not have been enough.
13. Dr Ceri Bygrave, for Myeloma UK and the UK Myeloma Society, asked whether flexibility may have been more prominent for the committee that appraised breast cancer in the context of that being one of the most common cancers. Dr Bygrave asked that NICE not allow process to cause a detriment to patients. Myeloma UK and the UK Myeloma Society consider that the committee should have applied flexibility and seen myeloma as being as relevant to patients with myeloma as breast cancer is to breast cancer patients. Dr Bygrave stated that three drugs will always be more expensive than one, that isatuximab with pomalidomide and dexamethasone is the only triplet combination for its type and that there is a danger if the FDG is published that it will be extremely hard to access triplets at fourth line. Dr Bygrave also acknowledged that the Systemic Anti-Cancer Therapy (SACT) data, like all real world data, is not ideal, and indeed did not include Welsh patients, many of whom Dr Bygrave had treated with isatuximab with pomalidomide and dexamethasone and benefitted.
14. Richard Diaz, for NICE, stated that the reason that the committee was able to flex in TA509 was because the ICERs in that appraisal were just above NICE's threshold and a full end-of-life weighting was not needed. There was no factoring of the treatment being for breast cancer as opposed to myeloma, that is completely independent, and NICE's committees will all acknowledge that all patients must be treated equally. If exceptionality were applied in every case then nobody would be treated equally. Richard Diaz further stated that pomalidomide is manufactured by a different company, and that the challenging circumstances of this evaluation probably could have been addressed in accordance with a Competition and Markets Authority (CMA) statement, worked on by NICE and NHS England, through a conversation between Sanofi and the manufacturer of pomalidomide.
15. Helen Knight when asked if NICE gave thought to transitional arrangements for the current Manual, stated that NICE was very clear about how the 2022 Manual would be implemented, including that the Manual would apply to all appraisals for which the invitation to participation was after 1 February 2022 and that a managed access exit appraisal would be treated like a new appraisal. This was discussed at industry events. Helen Knight said that NICE recognised that situations like this could be challenging. Helen Knight further stated that NICE had identified no adjustment that would have resulted in a positive recommendation here. NICE had to apply NICE's new methods as best practice but it also worked through the particular circumstances as best as it could. Helen Knight stated that paragraph 4.4.16 of NICE's Manual was inserted as a result of consideration during NICE's methods review of the challenge of treatments being not cost effective at zero price. NICE also considered during the methods review if a higher ICER threshold should be accepted or QALY weight applied in these circumstances, but it found no evidence that that would be supported. In this case, Sanofi say that isatuximab with pomalidomide and dexamethasone is not cost effective at zero price because of the combination with the comparator. NICE considers it clear that is a commercial challenge. NICE are asked to judge if the totality of an intervention is cost effective versus the comparator. NICE tried to work through specific issues but there was nothing it could do.
16. Dr Charles Crawley stated that the committee went into the evaluation aware that isatuximab with pomalidomide and dexamethasone may not be cost effective at zero price, largely driven by pomalidomide costs, so it looked at potential generic pomalidomide costs. There were some scenarios that might have allowed isatuximab with pomalidomide and dexamethasone to be cost effective but these were unlikely and the committee, having considered them, could not base a decision on them.
17. Sarah Love stated that the NICE representatives had suggested flexibility has to be binary and that the committee had not used flexibility available to it because it had considered the gap to be too great; however, if flexibility is not shown during the course of an evaluation in dialogue it is not known what avenues have been closed off. NICE has stated that some of the scenarios may have been cost effective. If NICE says “no” it closes off an array of possibilities. Flexibility isn’t an 'all or nothing'. It is not right for NICE to say that if it cannot make a giant leap there is no point in exercising flexibility at all.
18. Turning to the company's appeal point 1a.2, Adela Williams, for Sanofi, stated that this point 1a.2 overlaps substantially with Myeloma UK and the UK Myeloma Society’s point 1a.2. Adela Williams stated that there were various challenges in this evaluation arising from isatuximab with pomalidomide and dexamethasone being a combination treatment and the change in NICE's methods. Sanofi view the latter as the most significant issue here as there is no way Sanofi can possibly address the issues. The changes in methods created an unfair and unbalanced process disadvantaging isatuximab with pomalidomide and dexamethasone compared with other drugs. In contrast, treatments appraised under NICE's old methods are protected even though they may be less cost effective. These concerns were raised in the consultation. There was reassurance given to companies that in appropriate cases adjustments would be made. But in this evaluation the combination drugs were assessed under a different ICER threshold, and that important factor must be taken into account in decision-making. Failure to adjust for this is unfair. While it is not uncommon for NICE to look at comparators that are not cost effective, in some cases where NICE has changed its approach this would result in continued use of a not cost effective treatment, contrary to the interests of patients and the NHS. While Sanofi understood that NICE's current methods would apply to the CDF exit appraisal, it had no option but to agree this as a condition for inclusion in the CDF, but it reasonably expected that the exit appraisal would be conducted fairly. It considers transitional arrangements would have been appropriate.
19. Adela Williams went on to say that the issue is not simply a commercial one. There is an obligation on NICE to produce useful and appropriate guidance. Guidance is not that if it rejects more cost effective treatment. Sanofi accept it is not known if pomalidomide and dexamethasone would be cost effective if evaluated under NICE's new methods, but it can say that the standards applied to pomalidomide and dexamethasone were very different to those applied to isatuximab with pomalidomide and dexamethasone and the resulting uncertainty should have been taken into account. Further, while representatives of NICE have explained in the discussion of Myeloma UK and the UK Myeloma Society’s point 1a.2 (as reported in this decision document above) what it tried to do due to the unusual circumstances, little of this appears in the FDG so it is difficult for stakeholders to assess or understand and they could not do so on the hoof in this appeal. Adela Williams emphasised the need for transparency.
20. Mersha Chetty, for Sanofi, stated that non reference case analysis is used in circumstances that may overlap with those justifying a severity modifier or end-of-life weighting but are not the same.
21. Dr Charles Crawley stated that transparency of process is not restricted to the FDG and that the submissions, reports and papers are all available publicly on NICE's website. Dr Crawley stated that the committee did consider flexibility. He stated that the appellants misunderstand the limits on what flexibility the committee can apply; a technology appraisal is a rules-based process, the committee do need to follow process and there is a limit to what it can do. The committee exerted as much flexibility as it could, it considered going further than in the FDG but, even then, it could not come to positive recommendation. That was why it did what it did.
22. Helen Knight agreed with Sanofi that while NICE can move the goalposts by changing its methods, the game (i.e. any given evaluation) must still be fair. Helen Knight stated that NICE feels it has been fair. Helen Knight noted that an exit review is about access for new patients, and those who start isatuximab with pomalidomide and dexamethasone during managed access may continue. Access for all other patients at the time of the exit appraisal must be subject to the new methods because NICE has to be fair across patients. The committee were aware of the issues and recognised this was particularly challenging and looked at flexibilities to give the topic the benefit of the doubt. This was fair to Sanofi and patients involved as well as everyone else who is impacted by NICE recommendations. NICE's role is to assess a topic versus established clinical practice, i.e., what the NHS is doing. When it makes a methods change it does not review previous appraisals; a committee cannot be tasked with commenting on whether comparators remain cost effective.
23. Adela Williams reiterated that Sanofi say the most important way that the evaluation was unfair was that the comparators were assessed at a different threshold from isatuximab with pomalidomide and dexamethasone and that raises issues about whether the resulting guidance is perverse as it deprives people of a potentially more cost effective treatment. It is difficult to say that is not unfair as this is an almost unique situation and in general there is a transitional arrangement. There should have been a mechanism in place to ensure isatuximab with pomalidomide and dexamethasone was not treated worse than other technologies. That makes common sense, rather than a rigid application of the change in methods.
24. Mersha Chetty stated that the challenge here is that one of the comparators, pomalidomide, is the backbone of the combination drug isatuximab with pomalidomide and dexamethasone; isatuximab is added to something that is cost effective under a different threshold.
25. Helen Knight stated that the unusual position with the comparators was why there was a CMA discussion (i.e. a discussion in line with the CMA statement of November 2023 outlining when the CMA will not investigate competing pharmaceutical companies exchanging information and entering into commercial agreements on combination therapies for NHS patients (the CMA guidance), following work by NICE and The Association of the British Pharmaceutical Industry (ABPI)). It would be difficult for NICE to be responsible for resolving the fact that other companies price their technologies in a particular way for an appraisal. It is not for NICE to resolve pricing for combination elements. NICE was not rigid and did explore flexibilities, but the flexibility needed was too big for the committee to feel comfortable that it was fair in the round. As to reasoning, NICE cannot include reference to every point considered by the committee in the FDG.
26. Richard Diaz stated that it is Sanofi's choice to add isatuximab to combination therapies, that NICE has worked with the ABPI to try to avoid these situations, and that Sanofi could have done something about this.
27. Dr Charles Crawley responded to Sanofi's argument for a transitional period by stating that there was a long period leading up to the introduction of NICE's new methods, including a consultation highlighting the removal of the end-of-life criteria prior to isatuximab with pomalidomide and dexamethasone entry to the CDF, so this was a gradual process albeit that the start point for the new methods was from a fixed time point.
28. Dr Charles Crawley stated that isatuximab with pomalidomide and dexamethasone is not standard of care. Dr Crawley stated that when a treatment becomes available through the CDF the patient and clinical community view this as standard, but treatments in the CDF are not routinely commissioned (but rather in managed access for a fixed time period with no assurance of long term commissioning) and are not included as comparators in NICE evaluations.
29. Dr Ceri Bygrave stated that the patient community very much sees isatuximab with pomalidomide and dexamethasone as standard care. Dr Bygrave added that she had been inundated with queries from clinicians and patients when news of the committee’s recommendation became known.
30. Dr Neil Rabin, for Myeloma UK and the UK Myeloma Society, agreed that isatuximab with pomalidomide and dexamethasone is standard care in his practice at fourth line for many hundreds of patients, though he appreciated from a NICE process point of view it may not be classified as 'standard of care'.
31. Helen Knight confirmed that NICE do not consider managed access drugs as comparators or standard of care. It understands the drug is used, as that is why the CDF was developed, and that it may be clinically effective. If isatuximab with pomalidomide and dexamethasone had been cost effective at the point of the entry appraisal then NICE would have recommended it for routine use rather than entry into the CDF (which is used where cost effectiveness is uncertain and NICE gives the drug the benefit of the doubt for a limited period of access). Where NICE is not sure if a drug is cost effective it would be wrong for NICE to use that drug as a comparator in other evaluations. NICE did not know at that point if isatuximab would be clinically or cost effective. Further, NICE do not know if isatuximab with pomalidomide and dexamethasone is the "most" cost effective, as suggested by Sanofi at the hearing. It understands that this is incredibly hard for patients who might otherwise have used it in the NHS in future.
32. Dr Ceri Bygrave conceded that when a drug moves from the CDF to routine commissioning the floodgates open and the cost to the NHS has no bounds, however she stated that it would be useful for NICE to clarify the magnitude of difference between the ICER threshold in this evaluation and the actual ICER for isatuximab with pomalidomide and dexamethasone, as this affects patients to such a degree that they deserve some clarity.
33. Adela Williams stated that when a drug goes into the CDF the company is required to make a commercial offer that is consistent with the drug being cost effective, so isatuximab with pomalidomide and dexamethasone was cost effective under NICE's old methods. Following a period of time in the CDF we now have more data, which nobody suggests indicates isatuximab with pomalidomide and dexamethasone is less clinically effective, yet isatuximab with pomalidomide and dexamethasone is not cost effective under NICE's new methods.
34. Richard Diaz stated that the ICERs are confidential and clarified that the plausible cost effective ICER for isatuximab with pomalidomide and dexamethasone at entry into the CDF was based on Sanofi's (rather than the committee's) preferred assumptions.
35. Nigel Spencer, for Myeloma UK and the UK Myeloma Society, stated that patients would tend to expect the treatment they are on to be the most cost effective and the most clinically effective, and that he would find it difficult to explain to other patients that NICE's decision in this evauation was due more to historical changes to NICE's processes. Patients understand that cost effectiveness is important but expect NICE's processes to enable them to receive the treatment that ticks the most boxes.
36. Dr Charles Crawley stated that patients are offered cost effective treatments as well as treatments that are being explored and evaluated, including through the CDF. So it is not true to say that all drugs available on the NHS at a given time are demonstrably cost effective.
37. Turning to Sanofi's appeal point 1a.3, Adela Williams stated that this is a discrete appeal point albeit that elements of it were discussed as part of the discussion on Sanofi's point 1a.2 and Myeloma UK and the UK Myeloma Society’s point 1a.2. Adela Williams stated that NICE has committed to evaluate all new active substances and it must do so fairly, so if the result of an evaluation is perverse then NICE should adapt its approach. Adela Williams stated that this has been recognised in previous evaluation and at a meeting of the Patient Access to Medicines Partnership (PAMP) on 1 March 2024 at which NICE had acknowledged a dialogue may be needed with stakeholders where methods and process changes may impact ongoing managed access agreements and consider reasonable company requests for adjustments to the guidance update process. However, it seemed that when the NICE team was advised that isatuximab with pomalidomide and dexamethasone would not be cost effective at zero price it decided that the evaluation was likely to be futile and should be terminated. NICE invited Sanofi to withdraw from the evaluation before ACM1. This indicated a rigid process without flexibility despite what we have heard today.
38. Richard Diaz stated that NICE considered whether to rely on the "futility provision" in its Manual to terminate this evaluation because the EAG calculated that Sanofi's own base case ICERs were not cost effective. NICE decided to exercise flexibility by continuing the evaluation as there was potential for Sanofi to explore options available to it, but that did not come to fruition; negotiations in accordance with the CMA guidance were not explored during that time. Richard Diaz stated that NICE had informal conversations with Sanofi regarding the challenges it faced and how NICE was trying to deal with these. Richard Diaz stated that the evaluation was not a fait accompli but rather Sanofi's own base case was not cost effective, and that this is an important distinction. Sanofi had asked the committee to deploy the full QALY weighting that it would have got if the end-of-life criteria remained part of NICE's methods. NICE could not do that lightly, and it decided that the extent to which that would have meant ignoring NICE's current methods would have been too great, to the detriment of other treatments being evaluated by NICE. NICE did however give isatuximab with pomalidomide and dexamethasone the medium 1.2 severity weighting and it did also consider the non-reference case analysis involving removal of background costs for context (Sanofi having asked the committee to use this for decision-making).
39. Helen Knight confirmed that the PAMP meeting was held on 1 March 2024 and minutes were shared. Whether NICE would apply flexibility was raised as a concern at that meeting and the response was provided in the meeting minutes. Helen Knight stated that NICE was clear about its implementation of the new methods and agreed that where possible NICE was receptive to conversations about adjustments. Helen Knight further stated that NICE attempted flexibility in this evaluation, but in the end it was unable to make a positive recommendation.
40. Adela Williams stated that Sanofi's understanding is that the NICE technical team (not the committee) had essentially written off this evaluation and that shaped the way it was carried out. Adela Williams accepted Sanofi had no evidence of this but Adela Williams stated that that normally Sanofi receives the EAG report ten days after making its submission but this took much longer here, and that NICE should not have suggested that Sanofi withdraw before discussing the possibility of flexibility. Adela Williams said that the first indication from NICE that Sanofi should consider withdrawing from the evaluation was in February 2023. To the extent that NICE was relying on Sanofi negotiating with the manufacturer of the comparator, Adela Williams stated that the CMA guidance was not published until November 2023 and Sanofi did try to negotiate after that date.
41. The appeal panel considered Sanofi's two points 1a.2 and 1a.3 together in their discussion alongside Myeloma UK and the UK Myeloma Society’s point 1a.2. They concluded as follows. The panel agreed with the appellants and the committee that the particular circumstances of this evaluation were highly unusual (and arguably unique). Specifically, the “backbone” product in the isatuximab with pomalidomide and dexamethasone combination therapy (pomalidomide) was appraised under previous NICE methods that included a QALY weighting for technologies given at the end-of-life. NICE's Manual no longer includes the end-of-life criteria and associated weighting, so the historic / existing appraisal of pomalidomide produced an ICER (once the end-of-life QALY weighting was removed) that was significantly above what would be recommended today. It was agreed at the hearing that this combination of factors was the main reason that it was hard to establish the cost-effectiveness of isatuximab with pomalidomide and dexamethasone, even at zero cost. The panel judged that this was an unintended consequence of the implementation of this change in NICE methods.
42. The panel were aware that effective technologies may not be cost-effective even at zero price and this does not usually mean that any adjustment to standard NICE methods is needed. However, in this highly unusual situation due to the combination of factors outlined above that arose as an unintended consequence of a change in NICE methods, the panel judged that the application of standard NICE methods gave rise to a perverse outcome.
43. The panel were aware that in public law, a public body adopting a policy or procedure must not fetter its discretion (i.e. stick rigidly to that policy in all circumstances) but rather should keep its mind open to the possibility of flexing its policy in exceptional circumstances. The panel accepted that when exceptional circumstances required them to do so, the committee should consider if fairness requires a departure from the Manual. The panel agreed that the circumstances of this evaluation were exceptional, so NICE should have considered the possibility of departing from its processes.
44. The panel agreed that NICE and the appraisal committee had made reasonable efforts to show flexibility to address this challenge. However, the panel were not persuaded that NICE had recognised that it could consider going beyond this in applying flexibility outwith their standard process. They noted Dr Charles Crawley’s concluding comment that the technology appraisal process is “rules based” and a letter sent from Helen Knight to Sanofi of 13 March 2024 that stated that NICE could not “set aside its methods” because “this would represent a significant deviation from the 2022 methods which apply to the appraisal of isatuximab.” On balance, the panel judged that NICE had fettered its own discretion by failing to recognise that it could, in exceptional circumstances, deviate from its policy and that this constituted procedural unfairness.
45. In reaching this conclusion, the appeal panel does not find that fairness *required* NICE to depart from its usual processes, nor that fairness required NICE to take all necessary steps to ensure a positive decision. Rather, the panel judged that fairness required NICE to recognise that they could depart from their usual processes and to consider whether this was the right approach in this particular case.
46. The panel did not agree that the committee was required as a matter of procedural fairness to take the same approach as the approach taken in TA509 (application of end-of-life criteria outside of the usual methods). The panel agreed with the committee’s view that the circumstances of these two appraisals were very different, so procedural fairness did not require consistency in this respect.
47. The panel therefore upheld the appeal on appeal point 1a.2 and appeal point 1a.3 by Sanofi and appeal point 1a.2 by Myeloma UK and the UK Myeloma Society.
48. The panel noted it would expect NICE to consider applying flexibility outside its usual processes because of the exceptional circumstances of this evaluation.

### Sanofi Appeal point 1a.4: NICE’s refusal to refer isatuximab for commercial negotiation was inadequately explained and deprived Sanofi of the possibility to reach a satisfactory outcome to this appraisal.

1. Adela Williams, for Sanofi, stated that NICE's decision not to refer isatuximab with pomalidomide and dexamethasone for commercial negotiation conflicts with section 5.9 of the Manual. Adela Williams stated that section 5.9 requires NICE to seek formal confirmation from NHS England that it would be willing to discuss a commercial access agreement after the committee meeting if there is an indication that a technology is not cost effective. Adela Williams said that NHS England was willing to engage with commercial negotiations and that the committee disregarded Sanofi's requests. This was inconsistent with fair procedure. Adela Williams explained that Sanofi was contacted by NICE with a list of conditions for a proposed brief to support commercial negotiations (a commercial brief) but was surprised when on 25 April 2024 it received a call to say that NICE had decided not to refer isatuximab with pomalidomide and dexamethasone for commercial negotiation and that it would be issuing a negative recommendation. Adela Williams stated that this decision was made without any engagement or discussion with Sanofi or NHS England. Adela Williams stated NICE's position was contrary to NICE procedures and advice from the NICE technical team that Sanofi should consider a framework under the CMA guidance and undermined discussions between Sanofi and the manufacturer of pomalidomide.
2. Richard Diaz, for NICE, said commercial negotiation was not always required. Richard Diaz explained that NICE's commercial liaison team work with Sanofi and NHS England to deliver commercial arrangements and the committee's role is to provide the key assumptions so that commercial negotiations between Sanofi and NHS England can be held on a level playing field. Richard Diaz stated that the committee intended to go down the route of commercial negotiations and shared committee preferred assumptions with the commercial team. However, in the process of drafting the commercial briefing, it became apparent to NICE's commercial team that discussions between NHS England and Sanofi would not be fruitful. The commercial team decided (and informed the committee) that it could not write the brief as it would not be useful for the parties. Richard Diaz informed Sanofi of this on 25 April 2024 and Sanofi wrote back to confirm its understanding of the outcome and next steps. Richard Diaz said Sanofi did not ask for any further explanation. Richard Diaz also said he was unaware that Sanofi was planning to hold commercial discussions with the manufacturer of pomalidomide and that these discussions would be independent of Sanofi's discussions with NHS England. Richard Diaz stated that there was no reason why Sanofi could not pursue a conversation with the manufacturer of pomalidomide as soon as the CMA guidance was published, and had the committee been aware of discussions between those two companies – then that might have allowed the commercial team to prepare a useful briefing. Richard Diaz noted that due to the sensitive nature of commercial negotiations it is not appropriate to include commentary on this in the FDG but confirmed the committee did consider it in line with internal process.
3. Richard Diaz confirmed that NICE did seek formal confirmation from NHS England that it was willing to enter negotiations (per section 5.9.35 of the Manual). However, he said that when the commercial team started to write the brief it became clear that further discussions would offer no value and the decision was taken not to proceed.
4. Richard Diaz confirmed that the decision not to prepare a commercial brief was made by the NICE commercial team; it was not a committee decision. Richard Diaz explained that the committee is not privy to what happens in the commercial team and Sanofi can contact the commercial team without going through the committee. Richard Diaz said he was unaware if the commercial team warned Sanofi of its position in advance or if direct conversations happened.
5. Adela Williams stated that Sanofi repeatedly made clear it wanted to engage with NHS England and, if there had been dialogue, then it could have said it was seeking to discuss with the manufacturer of pomalidomide. Adela Williams stated that Sanofi received no further information and there was no communication on how to progress other options.
6. Anju Bhalla, for Sanofi, said Sanofi engaged as much as it could with the committee but was unaware it could engage directly with the NICE commercial team. Anju Bhalla explained that Sanofi did engage directly with NHS England up until March 2024, but this ended pending receipt of the brief (NHS England informed Sanofi it would contact Sanofi after it received NICE's commercial brief). Anju Bhalla stated that Sanofi wanted to work collaboratively with NICE and NHS England, knowing this was a challenging evaluation.
7. Mersha Chetty, for Sanofi, said that following NICE's decision not to proceed to commercial negotiation NICE told Sanofi they could appeal the FDG. Sanofi felt that without a commercial brief it was difficult to engage with the manufacturer of pomalidomide.
8. Richard Diaz stated that the commercial brief contains the committee's preferred assumptions for modelling and the levels of discounts that would be required to achieve cost-effectiveness. In this case it resulted in an ICER that was above threshold.
9. Richard Diaz asked whether any other creative solutions were considered, e.g. negotiations with the manufacturer of pomalidomide, stated that the brief only covers the current situation ('what is, not what if') and that any other options are for Sanofi and NHS England to discuss. Richard Diaz added that NICE and NHS England had no control over potential negotiations between Sanofi and the manufacturer of pomalidomide. Richard Diaz noted that Sanofi knew the preferred assumptions and could have created its own brief for discussions with the manufacturer of pomalidomide. It was for Sanofi to make an agreement with the manufacturers of the combination technologies if it wished and was able to do so. Normally this would be at an earlier stage before Sanofi made its submission to NICE, but it was still an option for Sanofi later down the line in this evaluation. Commercial discussions could happen at any time. Even now NICE monitors the landscape and could carry out a rapid review of isatuximab with pomalidomide and dexamethasone.
10. Anju Bhalla explained that Sanofi did start conversations with the manufacturer of pomalidomide, but it had taken discussions as far as it could without a brief from NICE.
11. Richard Diaz stated had he been aware of these conversations he would have enquired with NICE's commercial team as to whether there was anything else that could be done.
12. Helen Knight, for NICE, stated that commercial negotiations with NHS England would be very difficult as isatuximab with pomalidomide and dexamethasone was not cost effective at zero price. However, discussions between manufacturers of combination therapies and between NHS England and Sanofi do not require a commercial brief. Helen Knight said Sanofi had everything it needed (i.e. the committee's preferred assumptions). Helen Knight also noted that value attribution would not be included in the commercial brief.
13. Mersha Chetty, when asked why it could not pursue discussions without a commercial brief, said it was Sanofi's understanding that it required the brief as a formal document from NICE which established the evidence base for discussions.
14. Anju Bhalla said Sanofi was under the understanding that it needed the brief. She explained that Sanofi's conversations with NHS England had ended as it waited for the commercial brief.
15. Helen Knight stated that the commercial team was likely to be aware of the conversations between Sanofi and NHS England, but it cannot do a commercial brief for everything. Sanofi was provided with the assumptions and gave its agreement to them. It was only when the brief was being developed that it became clear it would be difficult to progress commercial negotiations.
16. Richard Diaz noted section 4.4.17 of the Manual provides for Sanofi to propose a commercial negotiation. Richard Diaz stated that this section opens the door for Sanofi to progress commercial arrangements.
17. Mersha Chetty noted that section 5.8.36 of the manual provides timelines and content of commercial briefings.
18. Richard Diaz stated that Sanofi had the preferred assumptions on 25 March 2024 and accepted them on 2 April 2024.
19. Mersha Chetty stated that whilst Sanofi accepted the assumptions it made clear it had done so only to move negotiations forward.
20. The appeal panel concluded as follows. The panel was aware that the price of pomalidomide was a key driver of cost-effectiveness of isatuximab with pomalidomide and dexamethasone in combination, and that commercial negotiation between Sanofi and the manufacturer of pomalidomide was an important potential mechanism to overcome the challenges faced in this evaluation. The panel noted section 5.9 of the Manual, which sets out the process around the role of NICE in commercial access agreements.
21. In this case, Sanofi and NHS England had agreed to enter commercial negotiations. The panel noted that Sanofi believed a commercial brief was essential to progress these negotiations, but NICE believed that conversations between the parties could continue with or without this document. The panel accepted that NICE had intended to support this commercial negotiation by providing a commercial briefing as set out in section 5.9.39 of the Manual. The panel heard that this was not provided because, in the process of writing the briefing, the commercial team formed the view that there was no potential to reach a cost-effective ICER. The panel noted that NICE had not been aware that Sanofi had started the process of negotiation with the manufacturers of pomalidomide (as allowed by the CMA guidance). The panel heard that, had the NICE team been aware of these discussions, and of the fact that the commercial briefing was felt to be vital to progress these negotiations, they may have reached a different conclusion on providing a commercial briefing to Sanofi and NHS England to support their discussions.
22. The panel felt that it was unfortunate that this issue had not been explored in more detail at an earlier stage of the evaluation process, and that poor communication seemed to have led to misunderstandings between the various parties. The panel judged that the Manual makes no *absolute* requirement for NICE to provide a commercial brief in these circumstances. The panel agreed that NICE advanced a clear reason for not doing so on this occasion: based on the information they had at the time they judged there was no possibility of reaching a cost-effective ICER. The panel noted that clearer communication between NICE and Sanofi might have helped to resolve this difficulty, but did not judge that this amounted to procedural unfairness. Nevertheless the panel strongly recommends that NICE reviews this section of the Manual to ensure that its interpretation is clear.
23. The panel therefore dismissed the appeal on this point.

### Sanofi Appeal point 1a.5: The Appraisal Committee failed adequately to consider the non-reference case analyses submitted by Sanofi.

1. Mersha Chetty, for Sanofi, said it is now well established that this evaluation could not demonstrate cost-effectiveness as part of a combination therapy. Mersha Chetty stated that recently attribution of value has been used to consider technologies in combination and that Sanofi had provided value attribution analysis to this evaluation. Mersha Chetty stated that the committee found the non-reference case interesting and informative but rejected it as there was no framework to consider it. This was unfair and it was incumbent on NICE to consider mitigation.
2. Dr Charles Crawley, for NICE, said there were two aspects to the committee's decision not to use value attribution methods. Firstly, the committee saw this as a commercial discussion between Sanofi and the manufacturer of pomalidomide. Sanofi considered isatuximab provided a high benefit and a low proportion of the cost of the combination isatuximab with pomalidomide and dexamethasone and in their view the ICER decision should be based on the relative cost and benefits of the component drugs. However, there was nothing in the Manual covering how this should be done and the committee had concerns about moving significantly outside NICE's methods. Secondly, Dr Crawley stated that – in any event – however costs were attributed between isatuximab and pomalidomide, attribution of value to each would not solve the problem faced by the committee in this evaluation unless pomalidomide were discounted. That is because the pomalidomide costs remain in the ICER for isatuximab with pomalidomide and dexamethasone. The committee had already concluded that the pomalidomide costs could not be removed in this evaluation because they were intrinsic to the treatment being evaluated. For these reasons a value attribution approach would not have helped the committee to find an acceptable ICER.
3. Mersha Chetty accepted that there was no framework but suggested the committee could have asked for advice from the EAG. Mersha Chetty noted that the omission from the FDG of any discussion of steps taken by the committee to address this appears to demonstrate that it did not make any effort to find a solution.
4. Dr Charles Crawley stated that in general there could be a case for value attribution when evaluating a combination therapy. However, the lack of a framework for doing so was problematic as this method could result in a committee arriving at an ICER for one component drug and another ICER for another component drug, and one of those ICERs might be cost effective, but NICE would still be unable to recommend the overall combination treatment as cost effective.
5. Dr Charles Crawley stated that the committee did not go back to NICE's technical support unit or to the EAG to enquire about methods for considering value attribution. This was mainly due to the timeframes of the evaluation.
6. Helen Knight, for NICE, explained that when NICE did the methods review there were discussions on whether to include value attribution. Those discussions, which included Sanofi, concluded that there was nothing further NICE could do. Helen Knight stated that the question asked of the committee was whether the technology is clinically and cost effective. The committee was not asked to drill down to which part of the QALY comes from each treatment. Helen Knight stated that pricing of combination elements of a treatment is considered a commercial issue and not something NICE does: if a committee stripped down costs and benefits of each component then there was a concern it would be getting into price setting.
7. Dr Ceri Bygrave, for Myeloma UK and the UK Myeloma Society, noted that myeloma is a unique cancer and that she was unaware of how many other cancer treatments are in combination. Dr Bygrave stated that synergy is important and the outcome can be more than the sum of its parts. Dr Bygrave said that any effort to take that apart is not clinically sensible.
8. Mersha Chetty acknowledged that this is a complex issue and it is difficult to address how you determine the value. Mersha Chetty explained that the value attribution analysis was an attempt by Sanofi to give the committee something to consider. Mersha Chetty stated there are previous appraisals where the committee paused the process to ask the EAG for help with a decision and that this could have been explored in this evaluation. Mersha Chetty stated that Sanofi would need NICE's assumptions in order to agree relative values of different parts of isatuximab with pomalidomide and dexamethasone.
9. Dr Charles Crawley stated that this would go beyond the DSU's interpretation of the Manual and would require significant updates to the Manual, which was outside the remit of the committee. Dr Crawley stated there was no requirement for a committee to approve a company's view on value attribution in order for that company to move forward with commercial negotiations; even if the committee had approved Sanofi's value attribution it would still have been open for discussion in commercial negotiation.
10. The appeal panel concluded as follows. There was agreement at the hearing there is nothing in the NICE Manual concerning the use of value attribution in the appraisal process. The panel noted that this had been considered by NICE in its most recent review of the Manual, and that NICE had decided that value attribution may be a useful approach for commercial negotiations but was not a useful part of the NICE appraisal process. The panel accepted that the committee had carefully considered the evidence on value attribution provided by Sanofi and given due consideration to whether they could use this. The panel judged that the committee’s reasons for not using this approach were clear, and that the decision not to consider value attribution could not be considered unfair.
11. The panel therefore dismissed the appeal on this point.

### Sanofi Appeal point 1a.6: The Appraisal Committee’s conclusion that it is unable to base its decision on removing the costs of pomalidomide and dexamethasone, because NICE recommends these products as cost effective misinterprets the Manual and improperly fetters its own discretion

1. Adela Williams, for Sanofi, referred to section 4.4.16 of the Manual which lists the circumstances when a committee can consider a non-reference case. Adela Williams noted that this included a non-reference case with the background costs removed in circumstances where the NHS was already providing the technology that is expensive or not cost-effective. Sanofi provided a non-reference case with the background costs removed which the committee said it would consider. However, the committee concluded it could not base its decision on the non-reference case because pomalidomide and dexamethasone was considered to be cost effective. Adela Williams said the committee had not interpreted the Manual correctly and had failed to consider whether current care is expensive and whether the cost effectiveness criteria could be met even if pomalidomide and dexamethasone had not been recommended. Sanofi does not suggest that NICE's recommendation in relation to pomalidomide and dexamethasone (TA427) is not of value but that when applying the test of cost-effectiveness to pomalidomide and dexamethasone in the context of a new evaluation this should be considered under the current processes. Adela Williams stated that it would be reasonable for the committee to remove background care costs as an example of flexibility, and the committee's conclusion that it could not adopt such an approach resulted in the committee fettering its discretion. Adela Williams concluded that the committee should have considered the non-reference case in more detail and it was incorrect for the committee to conclude that it could not consider such an approach.
2. Dr Charles Crawley, for NICE, stated that the committee did consider the non-reference case at length taking into account section 4.4.16 of the Manual. Dr Crawley noted that the guidance includes a criterion for removing the background care costs where they are driven by factors outside the intervention. Dr Crawley provided an example of dialysis in which costs are not directly linked to the intervention being evaluated Dr Crawley explained that the committee concluded that it would not be appropriate to remove the background costs in this case as they were directly linked to the combination drug being evaluated, isatuximab with pomalidomide and dexamethasone, and meant it could not create an ICER that was a true cost to the NHS. Dr Crawley stated that pomalidomide and dexamethasone may or may not be cost effective under NICE's current processes, but it had an ongoing NICE recommendation that it was cost-effective. Dr Crawley stated that the committee was mindful of a DSU report in 2014 which considered technologies that would not be cost effective even at zero price. Dr Crawley explained that everything should be included in the ICER. Dr Crawley noted that the same question was raised in the appraisal in 2020 when isatuximab with pomalidomide and dexamethasone entered the CDF and the previous committee said it did not see a way of removing costs and that this position was not challenged at the time. The committee did give the non-reference case consideration in this evaluation but concluded that it could not evaluate cost-effectiveness by removing these costs as this would exceed the flexibility which the committee was allowed.
3. Dr Charles Crawley acknowledged that the purpose of section 4.4.16 was to allow the committee to make a decision that it would not otherwise have been able to reach based on the reference case. The committee felt the non-reference case should be given proper consideration and explored whether there was scope to accept it, but the committee concluded it was unable to use it for its decision. Dr Crawley stated that the committee explored all possible approaches within the Manual as it relates to the use of non-reference costs but concluded that it could not remove the pomalidomide and dexamethasone costs.
4. Adela Williams said that Dr Charles Crawley's explanation is not reflected in the FDG. She said the FDG says the committee could not accept the analysis because of the previous appraisal and the reason given was solely that pomalidomide and dexamethasone had been assessed as cost effective.
5. Dr Charles Crawley explained that the FDG is not a verbatim script and said that if it is helpful the committee could clarify the explanation in the FDG.
6. Adela Williams said she appreciated it may be obvious to the panel and she appreciated the scope of the FDG but that it still needed to summarise the relevant reasoning and basis for decisions, or it is a pointless document. Adela Williams explained that if the reasons were not given then they do not form the basis for the decision making.
7. Helen Knight, for NICE, said the fact that the committee considered the non-reference case analysis demonstrated flexibility. Helen Knight explained that the criteria in section 4.4.16 are quite specific and that the committee considered the non-reference case analysis in line with those criteria. She apologised if the FDG was unclear.
8. Dr Charles Crawley said the committee did not know from the start that it would not use the non-reference case analysis but rather it considered whether it could do so and concluded that it was not in line with the Manual; he acknowledged that retrospectively he could not see how the committee could have reached a different conclusion.
9. The panel concluded as follows. It recognised that the committee had given detailed and serious consideration to the non-reference case analysis removing the background cost of pomalidomide. The panel noted that the Manual sets out at 4.4.16 the situations in which a committee may consider a non-reference case analysis with the background care costs removed. This states that a non-reference case analysis may be considered “in cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE’s normal levels”, a situation which clearly existed in the current evaluation. The Manual then sets out additional factors that the Committee should “*take into account*” when considering the non-reference case, in the four bullet points after the main body of 4.4.16. These include “if the high-cost care is separate from direct, intrinsic consequences of the technology” and “the extent to which commercial solutions would address the issues”. The panel agreed that both these factors were relevant to considering how much weight to place on the non-reference case analysis, and agreed that the committee had indeed considered them. The reason for the committee’s conclusion that it could not make its decision based primarily on the non-reference analysis, as set out in the FDG paragraph 3.17, was that this was because “pomalidomide and dexamethasone have been assessed to be cost-effective”. However during the hearing the committee chair explained that the principal reason was that they had concluded that pomalidomide and dexamethasone were “an intrinsic consequence of the technology” and therefore the costs could not be separated. In the panel’s view, the Manual requires only that this may be a factor to be taken into account, not that this represented an absolute barrier or a criterion that had to be satisfied in order to use a non-reference case as part of the evaluation. The panel therefore concluded that the committee had misunderstood the Manual and that this was unfair.
10. The panel therefore upheld the appeal on this point.
11. The panel noted it would expect NICE to revisit its consideration of the non-reference case analyses, bearing in mind the process set out in the Manual and the particular need for flexibility in this evaluation.

### Myeloma UK and the UK Myeloma Society Appeal point 1a.2: NICE has acted unfairly by neglecting to consider the significant impact that the 2022 update of the NICE methods and processes had on this appraisal.

1. There was substantial overlap between this point and Sanofi’s appeal point 1a2 and 1a3, and the panel considered these three points together. The panel concluded as set out in paragraphs 65-72 of this decision letter.
2. The panel therefore upheld the appeal on this point.

## Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers

1. There was no appeal points under this ground.

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

### Sanofi Appeal point 2.2: The inconsistent approach to modelling effectiveness of daratumumab is unreasonable

1. The appeal panel chair noted that appeal point 2.2 by Sanofi and appeal point 2.1 by Myeloma UK and the UK Myeloma Society covered similar grounds and would be taken together.
2. Sarah Love, for Myeloma UK and the UK Myeloma Society, noted that a central aspect of rational decision making is that decisions should be treated alike unless there is good reason not to. Sarah Love considered the previous appraisal, daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA783), to be comparable to this evaluation. Sarah Love noted that in TA783 the committee selected the Weibull distribution on the basis of its clinical plausibility. Sarah Love referred to paragraph 3.11 of the FDG noting that in the current evaluation the committee decided to choose the RCS log-normal 2-knot distribution as this was the EAG's preference. Sarah Love considered this to be problematic in three ways. Firstly, the Weibull distribution chosen by Sanofi had in the previous appraisal been agreed by the EAG as the most plausible. Secondly, the Manual does not provide a basis for taking a conservative approach for intervention versus the comparator and the touchstone should be plausibility whether considering a comparator or the technology under evaluation. Thirdly, the committee do not address the decision to take a different approach when considering the same data for the same condition. Sarah Love explained that she is not saying the committee cannot change its approach but that it needs a good reason to do so which is adequately explained in the FDG.
3. Dr Neil Rabin, for Myeloma UK and the UK Myeloma Society, stated that he was in attendance at both appraisal committee meetings. Dr Rabin said the available data set had not changed but the committee had interpreted it differently. Dr Rabin explained that at the ACM the clinical experts were asked about clinical practice and whether the committee should go with a different curve from previous appraisals. Dr Neil Rabin said he felt the current data overestimates the tail and he did not get chance to say this at the committee meeting.
4. Mersha Chetty, for Sanofi, said as a general principle the committee should take a consistent approach to the methodology, otherwise it becomes arbitrary and unreasonable. Mersha Chetty noted that in TA783 the committee agreed to use the Weibull curve and that since that appraisal no new evidence has become available. Mersha Chetty said the committee rejected the approach in TA783 and instead adopted the EAG's reasons to adopt a different statistical approach to the analysis. Mersha Chetty said the EAG noted no precedent for it and that the RCS log-normal 2-knot distribution had not been considered by Sanofi or EAG in TA783. In making this choice the committee had disregarded the advice of the clinical experts.
5. Dr Charles Crawley, for NICE, said that just because the committee had come to different conclusions it does not necessarily mean it is inconsistent. Dr Crawley noted that the RCS log-normal 2-knot distribution was not proposed or considered in TA783 and explained that the committee considered the RCS log-normal 2-knot distribution to provide a better fit. Dr Crawley acknowledged that the data had not changed but the analysis had, and the committee had a duty to look at it. He also noted that in this evaluation a conservative approach would not mitigate decision risk.
6. Dr Neil Rabin said it was not about best fit and he considered that the RCS log-normal 2-knot distribution was not clinically plausible when taking into account the number of people at 10 or 15 years.
7. Dr Daniel Gallacher, for NICE, noted he could not recall the exact clinical opinion, but it was clear that the log-normal distribution was a better fit. Dr Gallacher noted that it was plausible that had the RCS log-normal 2-knot distribution been considered in TA783 it would have been selected.
8. Mersha Chetty noted that sophisticated modelling analyses were available in 2021 when TA783 was appraised but neither the EAG nor the committee considered it necessary. In regard to whether RCS log-normal 2-knot distribution provides the best fit, Mersha Chetty noted that the extrapolation does not fit the start of the curve as well as the end and there is more uncertainty in the tail. Mersha Chetty also noted the issues raised regarding clinical plausibility and noted the SACT data was not as good as the information provided by clinicians.
9. Sarah Love said it was difficult to understand what advice the committee received on clinical plausibility and noted there is a risk of not recommending a cost-effective option. Sarah Love noted that in 2022 Weibull was chosen despite it not being the best fit but because of its clinical plausibility. She said the committee should take the world as it finds it, engage in what was done before and ask clinicians about plausibility.
10. Sarah Love said the fact the Weibull distribution had been chosen in TA783 was despite it not being the best fit and in view of its clinical plausibility, particularly the tail. She said that if the committee chose a different approach then it needs to provide a proper reason that engages with the reasoning of previous committees that considered the same treatment for the same patients.
11. Dr Charles Crawley explained that the committee considered a direct comparison of the two analyses and found the RCS log-normal 2-knot distribution to be marginally less pessimistic than the Weibull distribution and more pessimistic than the other models. Dr Crawley explained that at ACM2 the committee had advice from Sanofi on anticipated survival. Dr Crawley noted the RCS log-normal 2-knot distribution had an estimated 5-year survival of about 15% and the Weibull distribution 11.6%, both significantly below Sanofi submission of 25%. Dr Crawley said they were both within range suggested by Sanofi's clinical expert at 10 years.
12. Richard Diaz, for NICE, explained that the questions regarding the modelling were discussed at ACM1 and ACM2 and the appellants were also provided with an opportunity to provide comments during consultation on the draft guidance.
13. Caroline Donoghue, for Myeloma UK and the UK Myeloma Society, asked why the committee carried out new analyses when the model had been accepted by the EAG in TA783 and there was no change in data. Caroline Donoghue explained that the committee did not provide clinicians with any open questions on which model was more clinically plausible.
14. Dr Neil Rabin explained that he was aware of his opportunity to comment but said the direct question on clinical plausibility was never asked.
15. Richard Diaz said it was appropriate for the committee to consider advice from the EAG, weigh up the options and decide on its preferred approach.
16. Dr Charles Crawley said as this was a new evaluation it requires the committee to reevaluate all aspects. Dr Charles Crawley considered this to be the right approach and noted that if the committee just agreed with the previous approach it would be criticised. Dr Crawley noted that he did not recall the exact conversations on clinical plausibility but explained the committee would have given clinical experts an opportunity to voice their opinion.
17. Ross Wilkinson, for NICE, noted that given the content of the ACM1 slides which contain comparisons of the extrapolations it was unlikely that this was not discussed from a clinical perspective. He noted in response to Myeloma UK and the UK Myeloma Society that although in the previous appraisal the Weibull distribution was accepted as the most clinically plausible it was also acknowledged as conservative. Ross Wilkinson referred to section 6.2.33 of the Manual, which considers the possibility of decision error. Ross Wilkinson noted one way to take action is to take a conservative extrapolation. Ross Wilkinson noted that in this case taking a conservative extrapolation would not mitigate but increase the chance of that happening and paragraph 3.16 of the FDG acknowledges that the committee had likely represented the upper end of plausible values.
18. Sarah Love explained that the reason why Sanofi put forward the Weibull distribution was because of what happened in the previous appraisal. Sarah Love noted that the comments on consultation contain specific comments from Sanofi that there was no new evidence and the estimates were considered clinically plausible in TA783.
19. The appeal panel concluded as follows. It had heard that the Weibull distribution was selected for modelling in TA783 because it was the most clinically plausible of the distributions it was presented with and because a conservative approach reduced decision risk. In this evaluation, the committee was also presented with the option of using the RCS log-normal 2-knot distribution that had not been available to the committee at the time of TA783. The panel accepted that while the data had not changed since TA783, the options for analysis presented to the committee had changed. The panel judged that it was correct for the committee to consider all the options it was presented with. The panel noted the committee’s reasons for selecting the RCS log-normal 2-knot distribution: that it was the best statistical fit for the observed data, that the clinical evidence provided to the EAG agreed that it was plausible, and that choosing the most conservative approach in this evaluation (the Weibull distribution) would not mitigate decision risk. The panel agreed that these arguments were logical and reasonable. Although other approaches were possible, the committee’s reasoning made sense in the light of the evidence provided to them so the appeal panel did not find the committee's conclusion unreasonable.
20. The appeal panel therefore dismissed the appeal on this point.

### Sanofi Appeal point 2.3: The Committee’s approach to comparing the efficacy of isatuximab in combination with pomalidomide and dexamethasone does not reflect the evidence available and is therefore unreasonable

1. Mersha Chetty, for Sanofi, explained that Sanofi provided three data sets for considering the efficacy of pomalidomide and dexamethasone including a naïve comparison using SACT data. Mersha Chetty said this data set was dismissed by the committee because it considered it to be potentially impacted by confounding factors. Mersha Chetty said there was no evidence for this and both the naïve comparison and ICARIA data had similar baseline characteristics. Mersha Chetty said the committee chose to use the ICARIA data but failed to consider analysis from the EAG which produced similar results to that of the naïve comparison.
2. Dr Charles Crawley, for NICE, said that in general NICE considers randomised control data to be the best evidence of treatment effect. Dr Crawley noted that although the committee had concerns with the ICARIA data the committee did not consider the dataset to be particularly compromised. In contrast the committee considered there to be concerns with the data in Sanofi's naïve comparison based on the SACT data. Dr Crawley explained that naïve comparisons are by nature associated with risk of bias as no adjustment is made for differences in patient characteristics between the two data sources. Dr Crawley also noted that the SACT data is limited by the availability of baseline characteristics including both the range of characteristics and the missing data for the collected baseline characteristics. Dr Crawley said it was optimistic to consider adjustments to the SACT data and there was no reason why the committee should not adopt the randomised control data as the basis for relative treatment effect. Dr Crawley acknowledged that this did not mean the randomised control data were perfect, but the committee concluded there was no reason why naïve comparison would be preferrable.
3. Mersha Chetty referred to the evidence on the effectiveness of pomalidomide and dexamethasone. Mersha Chetty noted the SACT data does not need adjusting for subsequent treatment and that it was a good source of evidence for various reasons. Mersha Chetty said the pomalidomide and dexamethasone SACT data was the only source of clinical practice outcomes and that Sanofi considered the SACT data to be good evidence to compare pomalidomide and dexamethasone against isatuximab with pomalidomide and dexamethasone. Mersha Chetty accepted there were limitations but said those limitations would be the same across all SACT data. Mersha Chetty said the baseline characteristics are similar across pomalidomide and dexamethasone, isatuximab with pomalidomide and dexamethasone and daratumumab and that missing data was comparable across all three data sets. Mersha Chetty said there were a number of evidence sources provided to the committee which were either discounted as the committee had failed to consider the overall picture or for reasons that were not supported by the evidence. Mersha Chetty also noted that the committee accepted the constant hazard ratio but rejected the time varying hazard ratio which would have provided more accurate granular data to estimate the effectiveness of pomalidomide and dexamethasone.
4. Dr Charles Crawley stated that the committee looked at all of the SACT data in detail when considering the absolute treatment benefit. Dr Crawley said the committee considered potential differences between the isatuximab with pomalidomide and dexamethasone and pomalidomide and dexamethasone populations given they were taken over different timelines and took into account subsets of the pomalidomide and dexamethasone data to try to identify the fourth line population. Dr Crawley noted the committee found it notable that the relative benefit for isatuximab with pomalidomide and dexamethasone was greater in the naïve SACT data than it was in the clinical trial. Dr Crawley said the committee found this was unusual and it raised concerns about whether it was comparing like for like. Dr Crawley explained that in the SACT dataset there were limited baseline characteristics such as age which did not reassure the committee that it had the same populations.
5. Dr Neil Rabin, for Myeloma UK and the UK Myeloma Society, agreed that phase 3 data is really important to understand the differential benefits of isatuximab with pomalidomide and dexamethasone over pomalidomide and dexamethasone. Dr Rabin said there are reasons why the ICARIA data may overestimate the benefits for pomalidomide and dexamethasone whereas the SACT data may be an underestimation. Dr Rabin felt that the reality was probably between the two but accepted that the committee had to make a choice.
6. Mersha Chetty stated that clinical opinion was really important but adequate weight should also have been applied to the real-world evidence.
7. The appeal panel concluded as follows. The panel understood the pros and cons of using the ICARIA randomised trial data versus the SACT observational data for modelling the efficacy of isatuximab with pomalidomide and dexamethasone as discussed at the hearing. The panel was aware that neither set of data is perfect, but that the committee should take a rational approach to deciding which it prefers for decision-making. The panel noted the advice in the Manual (section 3.3.2) that “for relative treatment effects there is a strong preference for high-quality randomised controlled trials”. In this case, the panel agreed that the committee had considered the totality of the evidence, and had carefully weighed the relative merits of the ICARIA data and SACT data before concluding that the ICARIA data was most appropriate. The panel also noted that the committee had not “dismissed” the SACT data, and indeed had used this data to help model the absolute treatment benefit. The panel concluded that the committee’s approach to decision making was reasonable.
8. The appeal panel therefore dismissed the appeal on this point.

### Sanofi Appeal point 2.4: The Committee’s conclusion that the early survival benefit for isatuximab in combination demonstrated in the SACT datasets is not plausible disregards consistent evidence from the ICARIA-MM trial and is therefore unreasonable.

1. The appeal panel chair noted that appeal point 2.4 by Sanofi and appeal point 2.3 by Myeloma UK and the UK Myeloma Society covered similar grounds and would be taken together.
2. Mersha Chetty, for Sanofi, referred to paragraph 3.4 of the FDG in which the committee dismissed the real-world SACT data explaining that it did not consider the early survival benefit curve to be clinically plausible. Mersha Chetty said that this decision disregarded the data from the ICARIA trial which had the same trend. Mersha Chetty explained that patients on pomalidomide and dexamethasone were more likely to achieve less than a partial response and myeloma patients with a poor response will have poorer outcomes. Mersha Chetty said that as a result earlier survival benefit was likely to be more pronounced and this was consistent with the SACT data. Mersha Chetty said the benefit is explicable scientifically and for that reason the committee's rejection of the real-world SACT data is unreasonable.
3. Sarah Love, for Myeloma UK and the UK Myeloma Society, said that in essence the SACT data best reflected how these treatments work in practice and that no adjustments were needed. Sarah Love acknowledged that the SACT data has its limitations and that the ICARIA data also had advantages but disagreed with the committee's conclusion that the ICARIA data is more robust. Sarah Love said in reality neither dataset is perfect and the relative effect may be understated in the trial data and overstated in SACT. Sarah Love said no one dataset stands out as the most robust evidence but said there must be another way forward without completely dismissing the SACT data noting the reality probably lay somewhere in between the two data sets.
4. Caroline Donoghue, for Myeloma UK and the UK Myeloma Society, said the reasons provided by the committee for dismissing the SACT data were incorrect. Caroline Donoghue said that differences in the timeline between the data sets would favour pomalidomide and dexamethasone but could have a detrimental effect on isatuximab with pomalidomide and dexamethasone as this data was collected during the COVID pandemic. Caroline Donogue noted myeloma patients were more prone to COVID and many patients had come off isatuximab with pomalidomide and dexamethasone earlier or had doses delayed or reduced.
5. Dr Neil Rabin, for Myeloma UK and the UK Myeloma Society, said the two data sets showed different results and could be considered as complementary but both with flaws. Dr Rabin considered the truth probably lay somewhere in between the two sets.
6. Charles Crawley, for NICE, said the committee recognised the speed of change in the SACT data noting that within two months there was a 12% difference between isatuximab with pomalidomide and dexamethasone and pomalidomide and dexamethasone. Dr Crawley explained that patients would likely only have received one cycle of isatuximab with pomalidomide and dexamethasone before that analysis and the committee concluded that this either meant isatuximab with pomalidomide and dexamethasone was very good or the pomalidomide and dexamethasone population was considerably frailer. Dr Crawley also noted the committee's concerns that the data sets were collected over different time periods and the comparative data was unavailable. Dr Crawley noted that the pomalidomide and dexamethasone data showed worse survival which made the committee very uncomfortable about the validity of the naïve comparison. Dr Crawley explained that the committee did use the data for absolute treatment benefit which it considered to be the appropriate way to use the real-world data rather than assuming the real-world isatuximab with pomalidomide and dexamethasone had substantially greater effect than it does in a clinical trial.
7. Dr Charles Crawley, when asked if he had considered the table available in the papers that recorded the distribution of characteristics between the two datasets, explained that it was very limited and that age and ECOG [a scale that measures performance capability] were the only characteristics available. Dr Crawley explained that there were other characteristics were not available but would have been informative. Dr Crawley said the committee were aware of the pros and cons of both data sets and took both into consideration.
8. Caroline Donoghue challenged the committee's view that the early survival benefit with isatuximab with pomalidomide and dexamethasone indicated different populations. Caroline Donoghue noted the size and depth of the response and said the early survival benefit may be due to the speed of response in patients receiving isatuximab with pomalidomide and dexamethasone. Caroline Donoghue said the trend seen in both data sets could be explained clinically. She accepted that both data sets had pros and cons but said the committee did not need to pick one over the other and both should have been given weight.
9. Dr Charles Crawley explained that the committee did not discard any data but did come to the view that the uncertainty regarding subsequent therapies for the randomised control trial was much smaller than that for the naïve comparison.
10. Dr Daniel Gallacher, for NICE, said you cannot begin to look at the SACT data for relative treatment effect until you disregard the trial data. Dr Gallacher noted the datasets appeared similar on the basis of a handful of covariates and there was no evidence that they were vastly different. However, he had concerns with the SACT data as it was completed over a different time period, had missing data and patients were not randomised to groups. Dr Gallacher said it would have been inappropriate to use the SACT data when the committee had the randomised control data available.
11. Sheetal Fermahan, for Sanofi, referred to the earlier comments regarding the drop in survival rates in the first two months for patients in the pomalidomide and dexamethasone arm. Sheetal Fermahan said that whilst this may look implausible this trend is visible in both the SACT and ICARIA data sets.
12. Dr Charles Crawley noted that patients will be offered dexamethasone, pomalidomide and dexamethasone and isatuximab with pomalidomide and dexamethasone in different circumstances, for example, pomalidomide and dexamethasone will be offered to a less fit population. Dr Crawley noted that anecdotal evidence from the experts suggested there may be real differences between the patient populations.
13. Mersha Chetty said Sanofi tried to make adjustments to take into account the difference between the arms in the ICARIA data to account for subsequent therapies. However, the results were uncertain and if anything, counterintuitive. Mersha Chetty also noted that Sanofi provided a cycle-by-cycle time varying hazard ratio approach for relative treatment effect. She said this should have been considered and if the committee accepted that the relative treatment effect from the trial is plausible the committee should also have considered a time varying approach.
14. The appeal panel concluded as follows. The panel noted that the committee had been aware of the extent and speed of the survival benefit in the SACT data, and its conclusion this might reflect different characteristics of the treatment groups rather than a treatment effect. The panel did not find this argument unreasonable. The panel was also aware that this was only one of the factors considered by the committee in weighing the relative merits of the ICARIA and SACT data, and found that the committee had considered the totality of the evidence. As noted under Sanofi appeal point 2.3, the panel also noted that the committee had not “dismissed” the SACT data, and indeed had used this data to help model the absolute treatment benefit. The panel concluded that the committee’s approach to decision making on this issue was reasonable.
15. The appeal panel therefore dismissed the appeal on this point.

### Sanofi Appeal point 2.5: The inconsistent approach to assessment of utilities adopted in this appraisal relative to TA658 is unreasonable based on the evidence available,

1. This point was discussed alongside Myeloma UK and the UK Myeloma Society’s point 2.4.
2. Caroline Donoghue, for Myeloma UK and the UK Myeloma Society, stated that it is a core principle of technology appraisals to use the best available evidence. Myeloma UK and the UK Myeloma Society believe that the best data on utilities is the quality-of-life data from the ICARIA-MM trial, which is the only data available, and sees no reason why that data was dismissed by the committee.
3. Dr Neil Rabin, for Myeloma UK and the UK Myeloma Society, stated that utilities were extremely well captured in the ICARIA data and that this had good clinical plausibility and was the best data that NICE would ever have. Dr Rabin stated that this is a randomised data set capturing the data that NICE wants and providing a plausible way of understanding it in terms of depth of response and the psychological impact of disease response.
4. Nigel Spencer, for Myeloma UK and the UK Myeloma Society, emphasised the importance of complete response and the huge psychological impact of feeling that your body is not battling cancer. Nigel Spencer stated that patients were likely to have substantial difficulty with pain, remission and relapse, and that anything giving stability affects how patients view life and the future. He stated that full and partial remission are quite different and expressed shock and horror in response to NICE's negative recommendation, which he said seemed to patients a big step backwards at a time when the direction of travel for myeloma treatment has been positive.
5. Mersha Chetty, for Sanofi, stated that Sanofi's method was similar to that used in TA658 (i.e., the entry appraisal for isatuximab with pomalidomide and dexamethasone), involving the same disease and EAG. At that time the committee accepted different utilities for the different treatment arms. In this exit appraisal Sanofi used NICE's updated methods and the ICARIA data and the committee decided the same utility should be used irrespective of treatment. Sanofi consider the committee's approach was inconsistent with the previous appraisal TA658, the data and the opinion of experts.
6. Dr Charles Crawley, for NICE, stated that the committee had no difficulty using ICARIA data for the utility values but the question was whether to use treatment specific utilities or treatment independent utilities. This was a new evaluation and the committee was not bound by TA658 but rather had to reconsider from the beginning. Sanofi's model only considered treatment specific utilities. The EAG considered both that and treatment independent utilities, and the EAG found the latter provided the best fit and simpler modelling. Dr Crawley stated it was possible to argue either way, on a clinical basis, for isatuximab with pomalidomide and dexamethasone having advantages or disadvantages, but that for data modelling the committee felt the best approach was to use treatment independent utilities.
7. Dr Charles Crawley, when asked about the wording of paragraph 3.12 of the FDG (in particular the discussion of whether complete response would result in a greater reduction in symptoms and the committee's conclusion that it "recognised the psychological benefit to patients of knowing they have had a deeper response. But it was not convinced that a complete response would lead to better control of symptoms"), stated that while psychological symptoms are a type of symptoms, the committee did not have data to evidence better quality of life. The EAG did see benefit and the committee discussed this at ACM2 but there was no data showing psychological impact of depth of response so that remained unresolved. Dr Crawley added that the committee heard arguments both ways relating to isatuximab with pomalidomide and dexamethasone requiring additional hospital visits: this could reduce quality of life, but the committee also heard opinion that there was no difference in adverse effects and that people were happy to travel for the hospital visits. Therefore the committee did not suggest a quality-of-life disadvantage for isatuximab with pomalidomide and dexamethasone. Equally the committee did not see evidence that supported a difference in quality-of-life. Dr Crawley stated that there is a psychological benefit that is not captured in the clinical data suggesting putting greater weight on someone treated with isatuximab with pomalidomide and dexamethasone as someone else in the same health state. There may be a utility benefit of being in complete remission but it is not clear that this is significant enough to make a meaningful difference.
8. Dr Charles Crawley, when asked about Sanofi's table in its clarification response showing quasi-likelihood information criterion (QIC) and simplified QICu fit statistics in support of isatuximab with pomalidomide and dexamethasone improving utilities, confirmed that the committee saw that information. However, Dr Crawley stated that the EAG models assumed treatment independent utilities and that this suggested the EAG model was a better statistical fit.
9. Mersha Chetty stated that one of reasons the committee discounted any utility gain for isatuximab with pomalidomide and dexamethasone was that it saw no change from baseline over a period of time. Sanofi consider that was unreasonable because the data relied on by the committee covers a period of 15 months only (15 cycles), whereas in fact there is data on utility for 27 cycles, if using progression-free survival as a proxy for time on treatment. The committee had therefore unreasonably over-relied on the statistical model and dismissed the trial evidence.
10. Dr Daniel Gallacher, for NICE, explained that the committee agreed that the ICARIA trial data was relevant and its preference was to use the utility data from the trial. The question it faced was what to do with that data: use it to support treatment specific utility values assuming a higher quality of life for patients who had isatuximab with pomalidomide and dexamethasone or use it in treatment independent models? The latter provided a better fit and that informed the committee's decision.
11. Sheetal Fermahan, for Sanofi, stated that the data shows improvement in factors like pain and fatigue and that it was odd for the committee to use statistics on the issue of utility. She stated that isatuximab with pomalidomide and dexamethasone has demonstrated a deeper response and better symptom control, with disease burden and organ damage reduced, meaning that isatuximab with pomalidomide and dexamethasone does have a bigger impact on quality of life than other treatments.
12. The appeal panel concluded as follows. This point concerned the committee’s decision to use response-specific utilities rather than treatment-specific utilities for decision making. The panel heard cogent and strong arguments from the appellants in favour of using treatment-specific utilities (including that depth of response may improve symptom control and the potential psychological benefits of a full response to treatment). It heard that the committee had carefully considered both treatment-specific and response-specific utilities provided by the EAG and concluded that treatment-independent utilities had the best statistical fit. The panel judged that the committee had not dismissed the clinical expert evidence that deeper response might improve symptom control or have psychological benefits, but rather the committee had not been persuaded that the totality of the evidence supported favouring treatment-specific utilities. The appeal panel concluded that although a different committee could reasonably have reached a different conclusion on this point, the approach taken by this committee was not unreasonable.
13. The appeal panel therefore dismissed the appeal on this point. The panel noted that NICE may wish to review the comments on this issue in the FDG to ensure that they clearly represent how the committee reached their decision.

### Myeloma UK and the UK Myeloma Society Appeal point 2.1: NICE’s conclusion that the EAG’s (new) extrapolation approach for daratumumab was the most appropriate is unreasonable.

1. There was substantial overlap between this point and Sanofi's appeal point 2.2, and the panel considered these points together. The panel concluded as set out in paragraphs 139-140 of this decision letter.
2. The appeal panel therefore dismissed the appeal on this point.

### Myeloma UK and the UK Myeloma Society Appeal point 2.3: NICE’s conclusion that “the data from ICARIA-MM provided a more robust estimate of relative effect than the naïve SACT data comparison” is unreasonable.

1. There was substantial overlap between this point and Sanofi's appeal points 2.3 and 2.4, and the panel considered these points together. The panel concluded as set out in paragraphs 147 and 162 of this decision letter.
2. The appeal panel therefore dismissed the appeal on this point.

### Myeloma UK and the UK Myeloma Society Appeal point 2.4: NICE’s conclusion that “the same utility values should be used for each treatment arm” is unreasonable

1. There was substantial overlap between this point and Sanofi's appeal point 2.5, and the panel considered these points together. The panel concluded as set out in paragraph 176 of this decision letter.
2. The appeal panel therefore dismissed the appeal on this point.

## Conclusion and effect of the appeal panel’s decision

1. The appeal panel therefore upholds the appeal on the grounds Sanofi 1a1, 1a2, 1a3 and 1a6, and Myeloma UK and the UK Myeloma Society ground 1a2. The appeal is dismissed on all other grounds.
2. The evaluation is remitted to the appraisal committee who must now take all reasonable steps to address the concerns identified in the body of this letter, relevant to the respective appeal points which were upheld.
3. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE’s decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.