

21st September 2023

Dr Mark Chakravarty

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Dear Dr Chakravarty,

# APPEAL AGAINST THE FINAL APPRAISAL DOCUMENT: TEBENTAFUSP FOR TREATING ADVANCED UVEAL MELANOMA [ID1441]

Thank you for your letter dated 7th September 2023, in which you set out your preliminary views in relation to the admissibility of the points of appeal in our letter of appeal dated 31st August 2023.

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

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

# Appeal point 1(a).1: NICE acted unfairly by applying two criteria that it had already confirmed were no-longer appropriate, when it assessed whether tebentafusp should be routed to the Highly Specialised Technology (HST) programme. Consequently, tebentafusp was perversely routed through the Single Technology Appraisal (STA) programme, which is not intended for highly specialised health technologies and was unlikely to lead to a positive recommendation.

You express the view that NICE’s routing decision for a technology appraisal falls outside of the scope of this appeals process. We respectfully disagree.

First, it is evident from NICE’s appeals process guide that the routing decisions do fall within the scope of appeals. In particular, Section 4.2 of NICE’s appeals process guide confirms that appeals may relate to *“the way that the evaluation was done”*. Furthermore, Section 4.3 confirms that ground 1(a) *“relates only to the fairness of the process followed and not to the content of the final draft guidance.”* It is manifest that the routing decision is in fact *determinative* of the way the evaluation was done, because it decides the procedure by which the product is assessed, and therefore clearly falls within the scope an appeal.

To take one example, if an evaluation is performed under the STA procedure the standard ICER threshold is £30,000 (before end-of-life criteria), whereas if the evaluation is performed under the

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HST procedure the ICER threshold is £100,000. These different thresholds fundamentally affect how the evaluation is done. Consequently, if a routing decision is incorrectly decided, the entire evaluation is performed in accordance with the wrong process and the wrong criteria, which can, as in this case, cause significant unfairness and may lead to an erroneous recommendation.

Second, NICE’s routing procedure is legally part of the technology appraisal recommendation and high specialised technology recommendations procedures, pursuant to Regulations 7 and 8 of The National Institute for Health and Care Excellence (Constitution and Functions) and NHS England (Information Functions) Regulations 2013. This is confirmed, *inter alia,* by the fact that the HST criteria are part of the Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, and by the fact that this procedure was issued pursuant to Regulation 8(8) *“NICE must establish a procedure for the appraisal of highly specialised health technologies, and must consult such persons as it considers appropriate in establishing the procedure…”* - there is no other legal basis for NICE’s routing decision. Accordingly, the routing process forms an integral part of the technology appraisal procedures and Immunocore, as a (legal) person aggrieved by the recommendation, is entitled to bring an appeal *inter alia* on grounds that *“in making the assessment that preceded the recommendation, NICE… failed to act fairly”*, pursuant to Regulation 9.

Third, it would lead to absurd results and it would defeat the purpose of the appeals procedure, created by statute, if the routing decision was excluded from the scope of appeals. If this were the case, it would exclude what is likely to be one of the most impactful aspects of the evaluation from review by an independent panel, which cannot have been the intention of the legislator.

Fourth, NICE did not communicate to Immunocore any other opportunity for Immunocore to appeal against the routing decision before an independent panel. The ‘challenge’ procedure, does not satisfy the legal requirements for an appeal panel pursuant to Regulation 10, does not observe the principles of natural justice in the decision-making process and constitute therefore a breach of due process, as it does not provide the opportunity for a fair trial by an independent and impartial tribunal as required by Article 6 of the European Convention on Human Rights.

Fifth, in Immunocore’s view, the unfairness of the routing decision in this case, which included the application of redundant criteria, is manifest. In all the circumstances, it would not be appropriate to exclude this ground of appeal from review by an independent panel as this would impair transparency and accountability of NICE’s decision-making processes, contrary to Principle 2 of the NICE Charter.

# Appeal point 1(a).2: NICE acted unfairly and inconsistently by refusing to accept Immunocore’s modelling methods, when they were consistent with what has previously been accepted by NICE in prior technology appraisals and are consistent with best modelling practice.

We made two arguments within appeal point 1(a).2, namely:

1. *The Committee was required as a matter of procedural fairness to accept Immunocore's modelling methods, and failed to do so; and*
2. *The Committee was required as a matter of procedural fairness to "provide adequate explanations of their decision-making", and failed to do so.*

Thank you for confirming that the second argument in this point appeal is admissible.

We note that you are not currently minded to refer the first argument, and we are grateful for your invitation for further explanation in this regard. To clarify, in this ground of appeal, Immunocore does not assert that ‘*the Committee was required as a matter of procedural fairness to accept Immunocore's modelling methods*’. Rather, the ground of appeal is that the Committee was required as a matter of procedural fairness to follow their own best practice.

As detailed in the appeal, the Company’s approach to modelling was consistent with NICE Technical Support Document (TSD) 21 on flexible methods for survival analysis (10), supported by (i) the publication by Palmer et al.: ‘*A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies*’ (11) which assists with choice of methods from TSD21; (ii) clinical experts; and (iii) it was consistent with previous NICE technology appraisals, including TA519 on pembrolizumab, the comparator (12). It was procedurally unfair for NICE not to take an approach that was consistent with TSD 21, Palmer et al and NICE’s previous appraisals such as TA519 for pembrolizumab; and in line with the scientific and clinical evidence submitted by the Company.

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

# Appeal point 2.1 it was unreasonable for NICE to exclude tebentafusp from HST on the basis of two redundant HST criteria.

You express the view that NICE’s routing decision for a technology appraisal falls outside of the scope of this appeals process. We respectfully disagree, for the reasons stated in our response to the rejection of appeal point 1(a).1. In Immunocore’s view the routing decision was unreasonable and can be challenged within the scope of the appeal.

The evidence presented in the submission demonstrates the TSOP decision was unreasonable given metastatic uveal melanoma (UM) is an ultra-rare condition with high unmet need for which innovative treatments such as tebentafusp provide a paradigm shift for patients. The decision to review tebentafusp under the HST routing results in an inequitable outcome for these patients in denying them treatment due to inappropriate criteria being applied to the evidence provided.

# Appeal point 2.3: The Committee’s conclusion that overall survival modelling is highly uncertain and standard parametric approaches are the most appropriate to apply to both treatment arms, cannot reasonably be justified.

Thank you for confirming that appeal point 2.3 is admissible and will be referred to the appeal panel. One argument was rejected under this appeal point: “*the Committee’s conclusion, in effect, does not add up because it will mean that in order for tebentafusp to be cost-effective using the NICE endorsed EAG modelling approach, it will have to be provided below the cost of providing tebentafusp in England, Wales and Northern Ireland’’.* This argument was rejected on the grounds that NICE is not obliged to recommend a technology as cost effective for use within the NHS solely because that technology is priced at or below cost price.

To clarify, in circumstances where NICE has concluded that a technology is clinically effective and life-extending, and the Committee’s decision between two alternative models may be finely balanced, it unreasonable for NICE fail to take into account the fact that the Committee’s preferred model (which is challenged for multiple reasons) would mean that tebentafusp could never, in any circumstances, be considered cost-effective, because it would require the technology to be priced- below cost. A model that leads to such an outcome is inherently implausible and is inconsistent with the fact that tebentafusp is funded in many other countries across Europe. The Committee unreasonably failed to take into account the implausible outcome of their preferred model on the cost-effective price which resulted in unreasonable and unsustainable economic outcome.

# 2.4 In the context of an appraisal of a medicine for an ultra-rare disease, it is not reasonable for the Committee to reject the Company’s model on the grounds that the decrease in hazards is based on only a limited number of people.

Ultra-rare diseases such as metastatic uveal melanoma show a clear decrease in patient numbers at risk over the course of treatment. As noted in the appeal letter, in the tebentafusp arm there are the following number of patients at risk: 46 at 27 months, 32 at 30 months, 22 at 33 months. This is because tebentafusp is a treatment for a very a rare disease for which survival outcomes are poor. The already small patient numbers decrease over time due to death. The Committee is insisting on an unachievable level of analysis on a data set which does not exist for such an ultra- rare disease. The Committee’s focus on number of patients at the tail of the KM curve is, therefore, misplaced, as this tail off is to be expected given (i) the rarity of the condition and (ii) the life- threatening nature of the condition.

Moreover, guidance on best practise for modelling survival for immunotherapy treatments recommends that flexible approaches better capture complex survival functions with hazards varying over time as stated in the NICE endorsed Technical Support 21. This is because standard parametric models are limited in the shape of hazard they can represent. Additionally, the mechanism of action of tebentafusp is unique and translates to pseudo-progression and delayed response as has been observed with other immunotherapies. This aligns with the biphasic hazard observed in the data and presented to the Committee. Therefore, the conclusion that standard parametric models are more appropriate is wholly unreasonable given the evidence presented.

# 2.6 The Committee’s apparent endorsement of a monthly best supportive care costs model, without justification, and the Committee’s rejection of an evidence-based and expert supported one-off aggregated cost model, cannot reasonably be justified.

It was not clear in the FAD that the committee had retained their stated preferred approaches that were outlined in the ACD after the first committee meeting. In the ACD the suggestion to add these costs on an ongoing monthly basis was not one of the committee’s preferred assumptions. Inclusion of ongoing monthly costs similar to a ‘*one-off*’ cost does not reflect the reality of patients experiencing longer-term survival benefit with tebentafusp. Moreover, patients with metastatic uveal melanoma do not require best supportive care until the last 3-6 months of life. The company consulted with clinicians on this subject, and all confirmed that this is the case. While the FAD recognised that this had a limited impact on the cost-effectiveness results, the conclusion that there was uncertainty is unreasonable given that the ERG failed to consult expert clinicians on their preferred assumptions and the Committee appear not to have taken into account clinical experts’ comments on this in the second committee meeting that clearly reinforced the approach presented by the Company.

# 2.7 The EAG and the Committee’s preferred scenario is unreasonable because it would require tebentafusp to be provided below-cost in order to be cost-effective. This is inconsistent with NICE’s obligations to support innovation and does not reasonably take into consideration the fact that advanced uveal melanoma is an ultra-rare disease with only 100 patients per year expected to be eligible for tebentafusp.

The appeal letter presented three arguments on appeal point 2.7, namely the Committee’s decision to apply standard parametric modelling to overall survival is unreasonable because:

1. "*the price of tebentafusp required to be cost-effective would be below-cost price*";
2. it "*is inconsistent with NICE’s obligations to support innovation*"; and
3. it "*does not reasonably take into consideration the fact that advanced uveal melanoma is an ultra-rare disease with only 100 patients per year expected to be eligible for tebentafusp, and does not recognise the vulnerability of the very small patient group facing terminal disease without other proven treatment options*."

Thank you for confirming that argument 3 in this point appeal is admissible.

Regarding argument 1 ‘*the price of tebentafusp required to be cost-effective would be below-cost price’* it is relevant to the Committee’s decision given that despite the evidence provided there are no circumstances using methodology accepted by the Committee that tebentafusp would be cost- effective. The FAD states that ‘*clinical trial evidence suggests that tebentafusp could increase how long people live and the length of time before their cancer gets worse compared with the usual*

*treatments offered*.’ And that ‘*Tebentafusp meets the criteria for a life-extending treatment at the end of life and is likely to increase how long people live’*. Given the Committee’s remit is to evaluate cost-effectiveness, it is therefore an illogical paradox that the Committee’s conclusion in this case is that tebentafusp cannot be cost-effective using their preferred modelling approach.

Regarding argument 2, we agree that the Committee states in the FAD (3.20) that they recognise tebentafusp is an innovative new treatment however, there is no suggestion that this is then accounted for in any way upon reviewing the evidence provided.

We thank you in advance for considering the Company’s submissions in this appeal. We hope that the matters set out in this letter have clarified our appeal and that you now agree that all points may proceed to a full hearing.

We are available to answer any questions you may have or provide further clarifications.

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