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28 September 2023

Dear Immunocore Ltd.

**Re: Final Appraisal Document — Tebentafusp for treating advanced uveal melanoma [ID1441]**

Thank you for your letter of 21 September 2023 responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I consider the ground 1(a) points and then the ground 2 points.

***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.

Having considered the additional arguments made in your letter of 21 September 2023, I remain of the view that this appeal point should not proceed to an appeal hearing. That is because the routing decision is taken before the appraisal process commences, and is not amenable to this appeal process.

To explain my reasoning, it may assist to summarise the applicable statutory framework. Regulation 7(9) of the National Institute for Health and Care Excellence (Constitution and Functions) and NHS England (Information Functions) Regulations 2013 ("the NICE Regulations") obliges NICE to establish a procedure for the appraisal of health technologies. Regulation 8(8) of the NICE Regulations imposes a separate obligation upon NICE to establish a procedure for the appraisal of highly specialised technologies. Regulation 9(2) provides that a person may bring an appeal against a recommendation made following an appraisal conducted in accordance with either (a) the technology appraisal process or (b) the highly specialised technology process. Regulation 9 does not provide a right of appeal against the *prior* decision, as to whether the technology appraisal process or the highly specialised technology process should be followed.



I note your point that the criteria for entry into the HST process were, at the time of the routing decision for Tebentafusp, set out in the Interim Process and Methods of the HST Programme (they are now contained in the separate NICE health technology evaluation topic selection: the manual). The Interim Process and Methods of the HST Programme was, however, clear, at paragraph 27, that the process for topic selection was (as it remains) separate from the appraisal process, with a decision on progression and routing taken by a delegation of individuals from NICE, the DHSC and NHS England, producing a recommendation to Ministers, which is then followed by a formal referral from Ministers to NICE. Only then does the appraisal, conducted by the appraisal committee, commence.

# 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.

Having considered the additional arguments made in your letter of 21 September, I confirm my view that your second argument under this ground is a valid appeal point, i.e. that the committee was required as a matter of procedural fairness to provide adequate explanations of their decision-making as to their preferred modelling assumptions and, arguably, failed to do so.

You have clarified that your second argument under this appeal point is that the committee was a required as a matter of fairness to follow their own best practice. In support of this argument, you draw my attention to NICE Technical Support Document (TSD) 21 on flexible methods of survival analysis. You argued that it was procedurally unfair for NICE not to take an approach that was consistent with TSD 21. I do not accept that argument, because TSD 21 is clear on its face that NICE is not obliged to follow it. It states, in the second paragraph of the document (on page 2) that:

*The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.*

Accordingly, I confirm my view that your second point (as restated in your letter of 21 September 2023) should not proceed to an appeal hearing.

***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.

For the reasons given above in respect of appeal point 1(a).1, I do not regard this as a valid appeal point. The routing decision falls outside of the scope of this appeals process.

# Appeal point 2.2: The Committee’s decision to apply standard parametric modelling to overall survival cannot reasonably be justified because it led to clinically implausible results, namely, in the EAG's model, the estimate of 5-year survival in the comparator arm is 4-fold higher than published historical data.

I confirm my view that this is a valid appeal point and will be referred to an appeal panel for hearing.

# 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.

Having considered the additional arguments made in your letter of 21 September, I confirm my view that this is a valid appeal point and will be referred to the appeal panel, save for your argument that:

"*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 is inherently unreasonable and cannot be justified. Details of this calculation are provided in confidential appendix 1 of the appeal*."

In your letter of 21 September 2023 you clarified your argument here to be that "*it* [was] *unreasonable for NICE* [to] *fail to take into account the fact that the Committee's preferred model… would mean that* [for tebentafusp to be considered cost-effective] *it would require the technology to be priced below cost*". I do not accept that that is arguably unreasonable. The Committee is not obliged to take account of the production costs of the technology, in reaching its view on cost-effectiveness.

# Appeal point 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

Having considered the additional arguments made in your letter of 21 September 2023, I remain of the view that this appeal point should not proceed to an appeal hearing. That is because the premise of the appeal ground – that the Committee rejected the Company's model on the grounds that the decrease in hazards is based on only a limited number of people – is not supported by the wording of the FAD. I remain of this view for the reasons set out in my initial scrutiny letter.

I note the final sentence of your reponse argues that "*the conclusion that standard parametric models are more appropriate is wholly unreasonable given the evidence presented*". I consider that this is a valid appeal point under ground 2, and note that it is already covered by ground 2.3, as referred to the appeal panel.

# Appeal point 2.5: The Committee’s conclusion that the Company’s modelling overestimated the proportion of people surviving in the long term, because it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section is incorrect. This demonstrates that the Committee misunderstood the modelled survival data, and therefore the Committee’s conclusion cannot reasonably be justified.

I confirm my view that this is a valid appeal point.

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

Having considered the additional arguments made in your letter of 21 September 2023, I do agree that this is a valid appeal point, on the basis of your argument that the Committee did not take adequate account of clinical experts' comments on this in the second committee meeting that in your view reinforced the approach presented by the Company.

I will therefore refer this appeal point to the appeal panel as follows: "*The Committee's apparent endorsement of a monthly best supportive care costs model was unreasonable in the light of clinical experts' comments in support of a one-off aggregated cost model.*"

# Appeal point 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.**

I confirm my view that the following argument is a valid appeal point:

*The Committee’s decision to apply standard parametric modelling to overall survival is unreasonable because 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.*

Having considered the additional arguments made in your letter of 21 September 2023, I remain of the view that the following argument is not a valid appeal point:

*The Committee's decision to apply standard parametric modelling to overall survival is unreasonable because the price of tebentafusp required to be cost-effective would be below- cost price.*

In your letter of 21 September 2023 you contend that the Committee's conclusion is '*an illogical paradox*', because tebentafusp meets the criteria for a life extending treatment at the end of life and is likely to increase how long people live'. I do not agree. It is not paradoxical for a technology to meet those criteria and yet not be cost-effective. That of itself does not demonstrate any flaw in the model used by the Committee. I note that you have challenged the model on other grounds, which I have referred to the appeal panel.

Having considered the additional arguments made in your letter of 21 September 2023, I remain of the view that the following argument is not a valid appeal point:

*The Committee's decision to apply standard parametric modelling to overall survival is unreasonable because it is inconsistent with NICE's obligations to support innovation*.

In your letter of 21 September 2023 you acknowledge that the Committee states in the FAD (3.20) that they recognise that tebentafusp is an innovative new treatment. Your challenge, however, is that in your view there is no suggestion in the FAD that this is then accounted for in any way upon reviewing the evidence provided.

I note the Committee's conclusion in paragraph 3.20 that tebentafusp is innovative. I also note the Committee's conclusion in the same paragraph that "*all the health-related quality of life gains had been captured in the QALY calculations*." That being the case, there was no obligation on the Committee to apply further weighting to the innovative nature of tebentafusp when deciding whether or not to recommend it.

In support of my conclusion, I draw your attention to paragraph 6.3.3 of the Guide to the Methods of Technology Appraisal, which records that above a most plausible ICER of £20,000 per QALY gained, the Committee should exercise its judgement to take account of the following (amongst other things):

* *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.* (emphasis added)

Conclusion

Therefore the valid appeal points are:

* 1(a).2; NICE has failed to act fairly because the committee was required as a matter of procedural fairness to provide adequate explanations of their decision-making as to their preferred modelling assumptions and failed to do so.
* 2.2: The Committee’s decision to apply standard parametric modelling to overall survival cannot reasonably be justified because it led to clinically implausible results, namely, in the EAG's model, the estimate of 5-year survival in the comparator arm is 4-fold higher than published historical data.
* 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.
* 2.5: The Committee’s conclusion that the Company’s modelling overestimated the proportion of people surviving in the long term, because it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section is incorrect. This demonstrates that the Committee misunderstood the modelled survival data, and therefore the Committee’s conclusion cannot reasonably be justified.
* 2.6: The Committee's apparent endorsement of a monthly best supportive care costs model was unreasonable in the light of clinical experts' comments in support of a one-off aggregated cost model.
* 2.7: The Committee’s decision to apply standard parametric modelling to overall survival is unreasonable because 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.

NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing.

NICE will be in contact with you regarding the administration of the appeal, which will be held orally.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman National Institute for Health and Care Excellence