

31st August 2023

Dr Mark Chakravarty

Lead non-executive director for appeals

National Institute for Health and Care Excellence 2nd Floor

1. Redman Place London E20 1JQ

Dear Dr Chakravarty,

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

**EXECUTIVE SUMMARY**

Immunocore Ltd. wishes to appeal the recommendations in the above Final Appraisal Document (FAD) on the basis that they cannot reasonably be justified from the evidence presented to the Committee and the process followed was unfair. This unfairness was not resolved by NICE despite prompt and repeated efforts by the Company. NICE has therefore fallen into error and its recommendation was wrong. According to the Committee’s preferred scenario presented by the Evidence Assessment Group (EAG), the price required for tebentafusp to be cost-effective would be below-cost price, meaning a price for tebentafusp that is less than the cost of providing it therefore making it inviable for Immunocore to provide it to patients. Consequently, patients in England, Wales and Northern Ireland will be denied an effective, life-extending treatment for advanced (unresectable or metastatic) uveal melanoma (UM) an ultra-rare disease, whilst tebentafusp is reimbursed and made available in other countries.

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

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.

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**.**

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

* 1. it was unreasonable for NICE to exclude tebentafusp from HST on the basis of two redundant HST criteria.
  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 EAGs model, the estimate of 5-year survival in the comparator arm is 4-fold higher than published historical data.
  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.
  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.
  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.
  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.
  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.

# INTRODUCTION

We provide background information below on advanced (metastatic or unresectable) uveal melanoma (UM) and tebentafusp to assist the Appeal Panel. This summary is not intended to replace the more detailed information provided by Immunocore in its original appraisal submission.

Advanced uveal melanoma

UM is an ultra-rare, highly malignant, and life-limiting disease that initially affects the vascular layers of the eye. UM is distinct from other melanomas in its molecular pathology and physiology, particularly skin melanoma, and is a disease of significant clinical unmet need.

Up to half of all patients with UM go on to develop metastatic disease (1). Following diagnosis of metastatic disease, the prognosis is poor with a 1-year survival rate of only ~50%. In 90% of patients the first metastatic site is the liver and eventual liver failure is the predominant cause of death from the disease (2). Prior to tebentafusp, no treatments for metastatic UM had demonstrated a survival benefit.

Tebentafusp is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)- A\*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Tebentafusp is the only treatment licensed specifically for advanced (unresectable or metastatic) UM (approved by the MHRA in June 2022, FDA in January 2022, and EMA in April 2022). The value of tebentafusp to patients has been recognised in a number of accelerated regulatory procedures including Breakthrough Therapy Designation and Fast Track designation by FDA, Accelerated Assessment by EMA, Promising Innovative Medicine (PIM) in the UK, and it has orphan drug designation in GB, EU and US. Tebentafusp treatment is now funded in France, Germany, Austria, Switzerland, Italy, and Finland.

Tebentafusp is a first in class and highly specialised treatment representing the first significant development in advanced UM treatment in 40 years, with a unique mechanism of action, comprising an ImmTAC® (Immune mobilising monoclonal T cell receptor Against Cancer) molecule. ImmTACs work by redirecting the body’s own T-cells (i.e., white blood cells) to recognise and kill the cancer cells and represent a completely new mechanism for anti-cancer therapy. The ImmTACs T-cell receptor end binds to a specific protein (gp100 in the case of tebentafusp) presented by a protein (HLA) on the surface of cancer cells, and the other end attracts the body’s own T-cells and brings them into direct contact with cancer cells so they can kill them.

The incidence of primary UM is 540 patients annually in the UK (3). The estimated incidence of metastatic UM patients is 50% of which half would be HLA-A\* 02:01-positive and thus clinically eligible to receive tebentafusp as per the licensed indication. This results in a pool ~100 patients per year. An early access programme for tebentafusp has been in place in the UK for 2-years to June 2023 and has provided tebentafusp free of charge to ~140 patients. This supports the incidence of advanced UM patients would be ~100 annually and highlights the high unmet need for an effective treatment for advance UM.

Ocular oncology is managed within a highly specialised service (NCBPS01H) Patients suspected to have UM are directed toward one of three highly specialised service centres for ocular oncology, which will confirm the diagnosis, and a specialist multidisciplinary team in UM will take the lead in the treatment pathway of the UM patient. After initial treatment for primary disease, patients face years of periodic liver surveillance and report experiencing constant fear

of disease recurrence, as highlighted by OcuMel and Melanoma Focus during the NICE appraisal process.

As no proven effective treatments targeted for metastatic UM were previously available, a wide range of treatments have been studied in clinical trials, including liver-directed therapies, systemic chemotherapy, immunotherapy (e.g., checkpoint inhibitors) (3, 4). Checkpoint inhibitors such as pembrolizumab are available as a treatment option because they are licensed for advanced melanoma; however, these were approved based on **skin melanoma** studies, which did not include patients with advanced UM; hence there are limited data to support the use of checkpoint inhibitors in metastatic UM. This reflects the distinctiveness of UM, particularly in its genetics, biology and clinical presentation compared with skin melanoma (5). Hence, tebentafusp was awarded an orphan designation specifically for the treatment of UM by the MHRA and regulators globally.

Before tebentafusp, no systemic therapies demonstrated a clinically meaningful survival benefit for advanced UM (1, 6). Fewer than 10% of patients achieve an overall response to these systemic treatments (3). Furthermore, there is no evidence that any of the currently available treatment options improve overall survival by a significant degree, with survival for metastatic UM being typically less than 12 months (4, 6-8).

Tebentafusp clinical efficacy

Tebentafusp has shown a sizable and meaningful improvement in overall survival as first or second line treatment used for metastatic UM. Treatment with tebentafusp is weekly and continues until confirmation of disease progression.

The phase 3 randomised controlled trial (study IMCgp-100-202) with overall survival as the primary endpoint demonstrated that treatment with tebentafusp in the first line setting reduced the risk of death from the disease by 49% (9). This is exceptional for an advanced cancer. The median overall survival for patients treated with tebentafusp was 21.6 months (95% CI: 19.1– 24.3), compared with 16.9 months (95% CI:13.1–20.5) for the comparator arm. The average duration of treatment with tebentafusp in the clinical trial was 10.3 months.

The comparator arm of the study was an investigator’s choice of therapies: pembrolizumab, ipilimumab or chemotherapeutic dacarbazine. A large meta-analysis (n=2,494) of treatments used for metastatic UM reported a median overall survival of just 12.8 months (95% CI: 0.59– 2.50) and an estimated 5-year survival for treatment in the first-line setting of less than 3% (4). Tebentafusp is the first therapy to have shown significant clinical benefit, particularly a survival benefit in the treatment of metastatic UM.

As there are currently no proven effective treatments for metastatic UM, there is a major unmet need for tebentafusp as a novel and effective treatment option for this ultra-rare life-threatening disease. The current UK clinical guidelines recommend clinicians consider offering tebentafusp to HLA-A\*02:01 positive fit patients with metastatic disease pending availability (2). Tebentafusp

was developed specifically for the treatment of metastatic UM, and will therefore set a new standard of care, offering the first and only licensed effective treatment option for HLA-A\*02:01 positive patients with unresectable or metastatic UM, providing a highly valuable new treatment option for this ultra rare disease.

# PROCEDURAL HISTORY OF THE APPRAISAL

**HST Application via the scope consultation**

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| --- | --- |
| **Date** | **Event** |
| July 2021 | The initial scoping document was for an STA. |
| 31 July 2021 | Response to the initial scope submitted by Immunocore stating its view why tebentafusp should be considered via the HST programme |
| 10 August 2021 | NICE advised that not all HST programme entry criteria were met citing the following as grounds for non-entry:   * The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS * The technology is expected to be used exclusively in the context of a highly specialised service * The technology has the potential for life long use |
| 20 August 2021 | Immunocore challenged the refusal of HST programme entry |
| 25 August 2021 | Meeting of Topic Selection Oversight Panel (TSOP) following initial challenge by Immunocore |
| 31 August 2021 | NICE advise Immunocore that the challenge was not successful again citing the failure to meet the following criteria:   * The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS * The technology is expected to be used exclusively in the context of a highly specialised service * The technology has the potential for life long use (though this had been downgraded to amber from red) |
| 14 September 2021 | Decision about HST programme entry again challenged by Immunocore |
| 21 October 2021 | TSOP meeting |
| 25 October 2021 | NICE informs Immunocore that TSOP decision confirmed routing to STA with the treatment now refused on two grounds: |

|  |  |
| --- | --- |
|  | * The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS * The technology is expected to be used exclusively in the context of a highly specialised service   TSOP has accepted that:   * The technology has the potential for life long use   NICE advise they will proceed under the HTA procedure. NICE did not provide any prior means to appeal this decision until the present appeal.  NICE advise that appraisal submissions were due one week later on 2 November 2021. |

**Single Technology Appraisal**

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| --- | --- |
| **Date** | **Event** |
| 16 April 2020 | The Department for Health and Social Care requests that NICE  carry out a Single Technology Appraisal of tebentafusp for treating metastatic HLA-A\*02:01 positive uveal melanoma. |
| 29 July 2021 | Scoping Workshop |
| 31 August 2021 | Invitation to participate in appraisal |
| 2 November 2021 | Immunocore Ltd. submitted STA dossier |
| 26 January 2022 | Assessment Report prepared by Kleijnen Systematic Reviews (KSR) |
| 2 February 2022 | Comments on the Assessment Report by Immunocore Ltd. |
| 10 May 2022 | Appraisal Committee Meeting 1 |
| 14 June 2022 | Appraisal Consultation Document (ACD) issued for consultation |
| 12 July 2022 | Immunocore submits response to consultation on ACD |
| 30 September 2022 | Immunocore submits revised section B3 in response to ACD |
| 4 July 2023 | Appraisal Committee Meeting 2 |
| 3 August 2023 | Committee meeting outcome shared with stakeholders |
| 15 August 2023 | Final Draft Guidance published |
| 31 August 2023 | Deadline for appeal |

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

**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.**

Tebentafusp is by definition a highly specialised health technology1 indicated for the treatment of an ultra-rare condition that should have been evaluated through the HST programme and not through the STA programme.

NICE, acting through the Topic Selection Oversight Panel (TSOP), acted unfairly by applying two HST routing criteria which NICE had publicly confirmed to be redundant. Specifically, in its final routing decision for tebentafusp dated 25 October 2021 (Appendix 3), TSOP concluded that tebentafusp did not meet the following two criteria:

1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
2. The technology is expected to be used exclusively in the context of a highly specialised service

However, two months earlier, in August 2021, NICE published its Review of the Topic Selection approach for health technology evaluation (Review) which confirmed that these two criteria were no-longer appropriate, and therefore were redundant.

In particular, the Review states that the criteria requiring the technology to be used exclusively in the context of a highly specialised service, “***has been removed*** *given the planned changes to commissioning structures along with the acknowledgement that in what commissioning structures a treatment is delivered by the NHS is not within NICE’s remit.”* (paragraph 54(IV)).

Similarly, NICE confirmed that the criteria that *“treatment will usually be concentrated in very few centres in the NHS”* was redundant, by replacing it with the criteria that the condition is “very rare”.

NICE unequivocally concludes that *“[t]hose technologies that meet the 4 criteria will be routed to the HST programme.*”, namely:

* 1. The condition is very rare defined by 1:50,000 in England

1 As defined in Regulation 2(1) of The National Institute for Health and Care Excellence (Constitution and Functions) and NHS England (Information Functions) Regulations 2013, i.e., a health technology intended for use in the provision of services for rare and very rare conditions, namely, for ocular oncology services (Schedule 4 (80), The National Health Service Commissioning Board

and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012.

* 1. Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications
  2. The very rare condition significantly shortens life or severely impairs its quality
  3. No satisfactory treatment options exist, or, if it does the technology is likely to be of significant additional benefit to those affected

NICE, acting through TSOP, acted unfairly by continuing to apply redundant HST routing criteria to tebentafusp. Had the redundant criteria not been unfairly applied, the Company strongly believes that it would have satisfied the criteria (see Appendix 2 for full details), and consequently would have been more likely to obtain a positive recommendation from NICE. The unfairness is amplified by the fact that NICE had already started to apply the new HST programme criteria to other products.

By way of illustration, in its final scoping decision in November 2021 (just one month after tebentafusp), NICE followed the conclusions of the Review and did not apply the criteria for a technology to be used exclusively in the context of a highly specialised service, when it routed Lumasiran (which was not used in the context of a highly specialised service) to the HST programme. NICE did not wait for the publishing of the ‘NICE health technology evaluation topic selection: the manual’ on 31 January 2022, before disapplying this criterion.

Further examples may be seen in the field of gene therapy. In particular, the Review confirmed the removal of the criteria for the technology to have the potential for lifelong use *“given the introduction of one-off treatments this criterion is also redundant.”* (paragraph 54(IV)). Again, NICE did not wait for the publishing of the ‘NICE health technology evaluation topic selection: the manual’ on 31 January 2022, before disapplying this criterion. Instead, there are at least three examples of non-life-long gene therapy products (voretigene neparvovec, onasemnogene abeparvovec and eladocagene exuparvovec) that have been routed through the HST programme.

It was right for NICE to disapply the redundant criteria following the publication of the Review - the Review itself noted that the HST routing criteria had remained unchanged since 2013 and had been subject to misinterpretation and confusion by stakeholders. It also noted that the criteria needed to be refined to make the outcome clearer, precise, predictable, and efficient for stakeholders and decision makers, and the Review’s conclusions were the product of a thorough consultation procedure which had concluded months earlier in April 2021.

Conclusion on Ground 1(a).1

In conclusion, it is unfair, and indeed perverse for NICE to reject tebentafusp from the HST programme on the basis of two criteria that NICE has already determined to be inappropriate and had decided their removal, especially in circumstances where NICE was already disapplying redundant criteria in the assessment of other products.

The consequence of this unfairness is that tebentafusp has been subject to an inappropriate and inequitable STA cost-effectiveness analysis, requiring a price that is below-cost price, meaning a

price for tebentafusp, treating an ultra-rare disease, that is less than the cost of providing it to the NHS therefore making it inviable for Immunocore to launch tebentafusp in the UK (Appendix 1). NICE fails to recognise that a higher ICER threshold is required to encourage research on, and innovation for, ultra-rare conditions, and fails to secure fair and equitable treatment access for the very small populations with ultra-rare diseases, to the ultimate inequitable detriment of patients with metastatic UM. Indeed, analysis under the STA is particularly inequitable and would be unlikely to produce a positive outcome because the comparator, pembrolizumab, is indicated for multiple indications (e.g., lung cancer and skin melanoma) for large numbers of patients and has a price for the NHS to meet a cost-per-QALY threshold of £20k - £30k. In addition, pembrolizumab is used for a long duration, hence the 2-year stopping rule for assessment of continuation. Hence, pembrolizumab is priced for a large population of patients. Coupled with the very short duration of treatment for pembrolizumab in metastatic UM because of the lack of or minimal efficacy, plus administration of pembrolizumab every 6 weeks, it is an exceptional challenge for tebentafusp to be cost-effective below an ICER threshold of £50,000 using the STA procedure.

Procedure

In terms of procedure, the Company took all available steps to challenge the unfairness in the routing process, including by twice challenging TSOP’s decisions, the second occasion being on 14 September 2021 following which it was reconsidered at an exceptional TSOP meeting on 21 October 2021.

Furthermore, the appeal procedure established under Regulation 9 of The National Institute for Health and Care Excellence (Constitution and Functions) and NHS England (Information Functions) Regulations 2013, and NICE’s appeals procedure, may only be brought after a technology appraisal recommendation, or highly specialised technology recommendation has been issued. It was therefore not possible for the Company to bring an appeal against the routing decision until it obtained a technology appraisal recommendation within the FAD.

## 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.

The Company’s approach to modelling was consistent with NICE Technical Support Document (TSD) 21 on flexible methods for survival analysis (10). The Company’s approach to the modelling methods was 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). Other technology appraisals that use a similar piecewise approach are described in the NICE TSD 21 (10).

Immunotherapies, by their mechanism of action, generate a delayed response, called pseudo- progression in many patients (13). There is a growing body of literature providing evidence that survival functions for patients treated with immunotherapies exhibit complex hazard functions

varying over time that may be better captured by flexible survival models. Palmer et al.(11) developed an algorithm to complement NICE TSD 21 and guide analysts in the selection of flexible survival models accounting for the specificities of survival functions observed with immunotherapies.

The Company provided supporting evidence for the choice of preferred assumptions (NICE ID1441 Addendum 2\_updated B3) including on modelling of longer-term survival, and sought clinical expert input on the choice of curve fitting for model extrapolation. In contrast, the EAG and the Committee have failed to comply with their requirement to provide adequate explanations of their decision-making. In particular, no justification and no reference to clinical input was provided for the EAGs approach to modelling or preferred assumptions. The reasoning behind the EAGs preferred modelling assumptions and disregard of TSD 21 and the companion selection algorithm by Palmer et al. (11) have not been provided. The Committee has also not provided any justification for that approach to be most plausible instead of flexible models described in TSD 21, therefore in this instance NICE have failed to follow their own best practice procedures on their commitment to transparency in the decision-making process.

1. **Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE**
   1. it was unreasonable for NICE to exclude tebentafusp from HST on the basis of two redundant HST criteria.

Notwithstanding Ground 1(a).1, NICE, acting through TSOP, was unreasonable to conclude that tebentafusp did not meet two redundant HST criteria, namely:

* + 1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.
    2. The technology is expected to be used exclusively in the context of a highly specialised service

As noted in Ground 1(a).1, by August 2021 NICE had acknowledged that these two criteria were redundant and no longer appropriate.

Nevertheless, in the Company’s view, tebentafusp satisfied the criteria to qualify for the HST programme because primary treatment and diagnosis of advanced UM was made in the three NHS England-designated highly specialised centres. As noted in the Review, the question of in which commissioning structures a treatment is delivered by the NHS is not within NICE’s remit. It was therefore unreasonable for NICE to conclude that the criteria were not on the grounds that treatment and use of tebentafusp could take place closer to the patients, sparing them the need to travel great distances.

Furthermore, or in the alternative, it was unreasonable for NICE to apply these criteria strictly in circumstances where it had flexibility in the application of the criteria (as acknowledged in the Review) and in circumstances where it was applying the criteria flexibly for other products e.g.,

Lumasiran, voretigene neparvovec, onasemnogene abeparvovec and eladocagene exuparvovec (see Ground 1(a).1).

This is particularly unreasonable in circumstances where the HST procedure is designed exactly for products such as tebentafusp, and without which research on, and innovation for, ultra-rare conditions would be stifled, and patients suffering from ultra-rare diseases, such as UM, would be treated inequitably:

*“31. Given the very small numbers of patients living with these very rare conditions* ***a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for companies in making a reasonable return on their research and development investment because of the very small populations treated****. Nevertheless, as part of its consideration of the value for money of the technology, the Committee must give consideration to the balance between the costs and the benefits.”* Interim Process and Methods of the Highly Specialised Technologies Programme (Updated to reflect 2017 changes)

## 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 EAGs model, the estimate of 5-year survival in the comparator arm is 4-fold higher than published historical data (4).

It was unreasonable for the Committee to accept the EAGs application of standard parametric modelling in circumstances where it led to clinically implausible results that were not substantiated by the evidence provided or validated by the clinical experts. This issue is critically important because the approach to modelling of the comparator arm (treatment with pembrolizumab) has a very large impact on the ICERs presented by the EAG. In the EAGs model, the estimate of 5-year survival in the comparator arm is 11.6% when survival at 5-years in published historical data is typically around 2.7%, which is clinically implausible in the absence of any treatment available with proven survival benefit.

The Committee has not explained or justified why it adopted the EAG’s assumptions in modelling overall survival in the comparator arm. In particular, the Committee has failed to explain why it accepted implausible 5-year overall survival estimates in the comparator arm and why it departed from the expert clinical opinion given at the second Committee meeting, which confirmed that, in the absence of any other treatment with proven survival benefit, it is not clinically plausible for survival to be this high in the comparator arm. Indeed, an independent clinical study on treatment of metastatic UM with pembrolizumab failed to report median overall survival because patient outcomes were so poor; survival was 12.8 months for patients with clinical benefit and 3.1 months for progressive patients (14).

The unreasonableness in the Committee’s approach is compounded by the fact it appears the EAG did not seek any clinical expert advice on the appropriateness of its modelling (as no such expert advice is mentioned in the ACD, FAD or Committee papers). Whilst at the same time disregarding the opinion of clinical experts who treat patients suffering from this ultra-rare condition and who concluded that the Company’s model correctly took a balanced approach to the comparator arm modelling with a 5-year overall survival of 5%.

The rejection of the Company modelling and the expert clinical opinion before them without consulting with clinical experts experienced in the management of rare and ultra-rare conditions is inexplicable, and unreasonable, as only experts in the field will fully understand the specific clinical pathways and can opine on the clinical plausibility of the health economic models required by NICE.

To quote section 4.3 of Guide to the technology appraisal and highly specialised technologies appeal process, the Committee’s acceptance of EAG’s estimates of 5-year overall survival in the comparator arm simply “does not add up”, is illogical and is fundamentally wrong. Accordingly, the Committee’s conclusion that a standard parametric approach should be used to extrapolate the data in both treatment arms cannot reasonably be justified.

## The Committee’s conclusion that standard parametric approaches applied to both arms are the most appropriate, cannot reasonably be justified

The Committee acknowledged that the Kaplan Meier (KM) curve and the hazard plots showed the hazard had increasing and decreasing trends, although noted that this was based on a low number of patients at risk. The Committee also acknowledged that “*the clinical experts explained tebentafusp has a novel mechanism of action. So, it is reasonable to assume that post- progression survival is different after tebentafusp than after immunotherapy, so using a different modelling approach in each arm may be reasonable” (FAD section 3.11).*

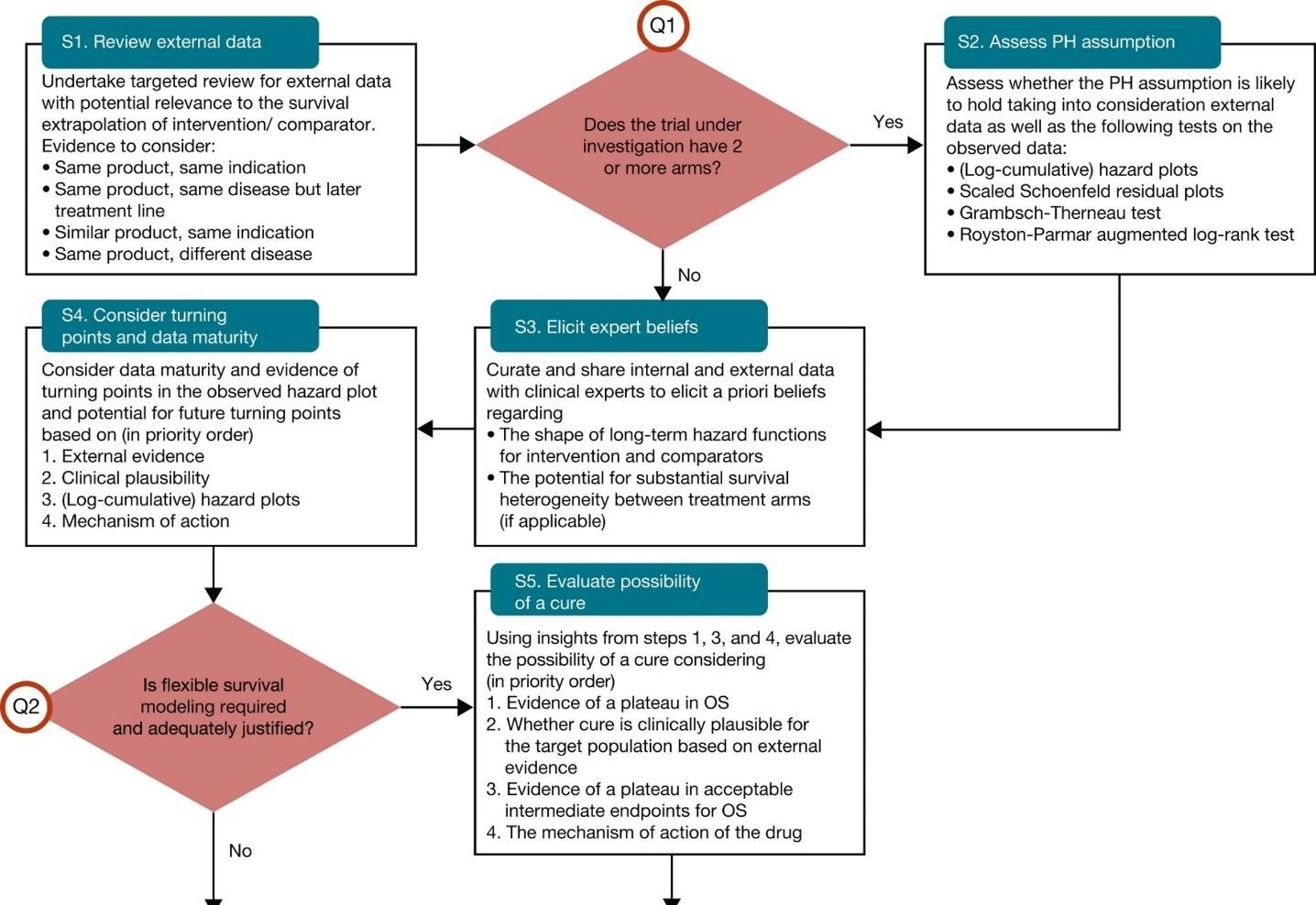
The Company based its choice of model on the algorithm for selection of survival extrapolation models for cancer immunotherapies by Palmer *et al*. (Figure 1) (11). Technical support document (TSD) 21 (10) provides a guide on flexible methods for survival analysis when time- varying hazards are encountered. The article by Palmer et al, was written to address a gap in TSD 21, by providing an algorithm to guide analysts on when to use flexible models and which to select. It recommends extrapolating the treatment and comparator arms separately. It also encourages analysts to consider the shape of the observed and the assumed hazards in the long term, to assess survival heterogeneity between the treatment arms and the potential for long-term survivorship, and to use clinical expert input. Following the steps of the algorithm, the Company concluded that a flexible model is more appropriate because of these algorithmic parameters:(1) there was evidence that the proportional hazard assumption may not hold; (2) the data and clinical experts feedback aligned on the fact that the survival functions were different between the arms; (3) the hazard plot was varying with time with a clear turning point; and (4) the mechanism of action of tebentafusp differed from that of pembrolizumab and thus

explained the differences in response. However, this seems to have been disregarded by both the Committee and EAG without providing any justification.

Despite Immunocore following best modelling practice, consistent with the similar piecewise approach used in other technology appraisals as described in the NICE TSD 21 (10), the Committee preferred to use standard parametric models in line with the EAG preferred assumptions. Once again, there is no documentation in the ACD or the FAD of the EAG seeking any clinical expert advice on the appropriateness of this modelling.

Given the above points and the fact that standard parametric models did not capture the plateauing of the curve and generated survival predictions which did not align with clinical expert’s feedback consulted by the Company, the Committee’s position has not, and cannot reasonably be justified. 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.

Figure 1. Flexible survival model selection algorithm – steps 1 to 5 (adapted from Palmer et al. 2023)



## 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.

**Section 3.11 of the FAD states that:** *“The Committee accepted that the Kaplan–Meier and hazard plots showed the hazards increasing and decreasing. But it noted the decrease in hazards was only based on limited number of people. So it was less certain of the factors that were driving this.”*

The Committee fails to recognise the inherent limitations of a rare disease. Despite the orphan nature of the disease, as recognised by the MHRA, the Company has managed to conduct a well-designed randomised controlled trial, powered to detect differences in overall survival; the gold standard for oncology medicines. Although the numbers at risk are inevitably lower at this point of analysis, the numbers included in the analysis are higher than seen in many trials of rare disease. 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. The Committee is requiring an unachievable level of analytical power for this ultra-rare disease. Whilst we understand the desire for decision-making to be as robust as possible, this further emphasises why the Company twice challenged the routing of this appraisal as an STA and highlighted that tebentafusp should have been routed through the HST process, which is designed to accommodate the inherent challenges in evaluations for innovative products for ultra-orphan diseases with no existing effective treatment options.

## 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 cannot reasonably be justified.

Section 3.11 of the FAD states that: *“The Committee concluded that the overall survival modelling was highly uncertain, but the Company’s approach appeared to overestimate the proportion of people surviving in the long term. This is because it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section.”*

This statement, and therefore the approach taken by NICE, is incorrect - the extrapolation models were adjusted for background mortality to ensure the survival probabilities in the model are plausible (NICE ID1441\_Addendum 2\_updated B3 CEM). The rate of death at any time point in the model for a population with metastatic UM cannot be smaller than that of the general population mortality for the same age group. Based on the Company’s model approach, piecewise lognormal, the mortality rate in the model for the first 13 years is based on the standard parametric lognormal model as it is larger than the general population background mortality. This demonstrates that NICE statement that “*it generated extrapolations suggesting that people did not appear to die in the period modelled by the parametric section.”* is incorrect. Beyond this point, as the rate from the lognormal model falls below that of the general population

background mortality rate, these are used instead to ensure the plausibility of the extrapolations. The Committee has fundamentally misunderstood the modelling and statements in the FAD about extrapolations are wrong and therefore cannot reasonably be justified.

## 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.

The EAGs preferred approach to applying best supportive care costs was monthly following disease progression as defined by the endpoint of progression-free survival (PFS) rather than as a one-off cost (as in the Company’s base case). The suggestion to add these costs on an ongoing monthly basis was not one of the Committee’s preferred assumptions in the ACD. Further, the Committee’s conclusion did not reflect the clinical evidence which demonstrates a clear disconnect between OS benefit and PFS, a result of which is that the treatment label is for discontinuation of tebentafusp is based on a clinical decision and not based solely on progression according to an increase in tumour size. Inclusion of ongoing monthly costs similar to a ‘one-off’ cost does not reflect the reality of patients who are experiencing longer-term survival benefit with tebentafusp as confirmed by the clinical expert in Committee meeting 2.

Moreover, post-documented progression, patients remain clinically well and are able to continue daily life, they do not require best supportive care until the last 3-6 months of life. The Company consulted with clinical experts on this subject, and all confirmed that this is the case.2 The Committee’s endorsement of this approach, which disregards expert opinion, therefore cannot reasonably be justified. In contrast, the approach the Company presented to NICE applied costs of best supportive care for the last 4 months of life as an aggregated cost covering this period, based on a well-referenced publication McKendrick *et al*. (15) on healthcare utilisation for late- stage melanoma patients [which was further endorsed by clinical experts].

## 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.**

2 Clinical experts were consulted on this in a meeting in July 2021

*Q: Is modelling QoL based on time to death appropriate in this population? Estimation of QoL based on time to death: at what point would you expect to see a deterioration in patients with metastatic UM?*

*A: The experts agreed that the decline in QoL is more about time to death rather than time of progression. Their expectation is that QoL will rapidly decline within the last 6 months of life.*

In view of Grounds 2.2–2.5, the EAG and the Committee’s decisions to nevertheless apply standard parametric modelling to overall survival cannot reasonably be justified, because the price of tebentafusp required to be cost-effective would be below-cost price. The EAG and the Committee’s approach therefore leads to a perverse and unethical outcome which is obviously wrong, irrational and 'does not add up'.

Such an approach discourages innovation, which is inconsistent with NICE’s obligations to support innovation in the provision and organisation of health and social care services in accordance with Principle 8 of the NICE Charter, in particular by encouraging interventions that provide substantial distinctive benefits that may not be captured by measuring health gain (that is, the estimated QALYs gained).

Furthermore, this approach 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.

# REQUESTED OUTCOME FOLLOWING APPEAL

Immunocore requests that the appraisal of tebentafusp is returned to the appraisal Committee for further consideration with the following directions:

* + 1. NICE review the decision to reject tebentafusp for Highly Specialised Technology (HST) routing, and prioritise appraisal of tebentafusp under the HST, utilising the evidence already provided in the initial submission and subsequent update of the submission.
    2. If the appeal panel refuses (1), the current FAD should be converted to an ACD and issued for consultation, for reconsideration considering the findings of the appeal panel.
    3. The responses to consultation on the new ACD (the current FAD) should be considered by the appraisal Committee when considering revisions to the draft guidance.
    4. In any event, the EAG should consult with a UM clinical expert, particularly in advanced UM with experience of tebentafusp in relation to its modelling.
    5. The Committee continue to consider the decision on tebentafusp in accordance with the NICE methods applicable when the assessment began, namely, Guide to the processes of technology appraisal Process and methods Published: 2 September 2014 Last updated: 30 May 2018.

# CONCLUSION

Immunocore requests that this appeal should be determined at an oral hearing.

We thank you in advance for considering the Company’s submissions in this appeal. We are available to answer any questions you may have or provide further clarifications.

Yours sincerely, Immunocore Ltd.

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