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18 April 2023

Re: FINAL EVALUATION DETERMINATION - AFAMELANOTIDE FOR ERYTHROPOIETIC PROTOPORPHYRIA (EPP) [ID927]

Dear Dr Chakravarty,

1. Introduction

1.1 We refer to your letter of 31 March 2023.

1.2 Thank you for your indication that a number of the grounds raised in CLINUVEL's letter of 24 March 2023 ought to be referred as appeal points to the Appeal Panel. CLINUVEL wishes to elaborate on, or clarify, a number of the points raised. The definitions in the letter of 24 March 2023 are adopted for convenience.

1.3 As a preliminary matter, CLINUVEL confirms that legal privilege is not asserted in respect of the contents of its 24 March 2023 letter and, as such, the 24 March 2023 letter should not have been marked as privileged. CLINUVEL maintains its claim of confidentiality in respect of the material redacted at paragraphs 4.3 and 9.17 and the letters of 16 March and 14 July 2022. The matters referred to in those paragraphs and redacted in those letters are either commerciality sensitive and confidential to CLINUVEL (i.e. concerning matters of pricing or negotiations in respect of the same) or relate to personal information and emails which have been redacted for privacy reasons. We do not consider the redactions to be disproportionate in the circumstances and expect that CLINUVEL's confidentiality is maintained. Please let us know if you have any concerns or questions in that regard.

1.4 Before addressing the grounds of appeal, we are grateful for the indication that CLINUVEL is entitled to seek a factual correction in respect of Appeal point 2.7, namely the erroneous description of the development of the EPP-QoL tool. We intend to seek confirmation at the Appeal hearing that the Committee agrees to this correction. Assuming that a factual correction is made, CLINUVEL is content not to pursue this point as a ground of appeal in its own right, but reiterates that it has made several requests to correct this error made by NICE over the course of the review since 2015, including in the draft ECD.

2. Appeal point 1(a).2: The requirement of 'conscientious consideration' was not met

2.1 CLINUVEL considers that, when the matters raised in its letter of 24 March 2023 (in particular, under Appeal points 1(b) and 2.4-2.6) are taken in the round, it is clear that the Committee was not willing to seriously contemplate a change of course.

2.2 There are two particular matters that, in CLINUVEL's submission, illustrate this procedural failing.

2.3 The first is the position that NICE has taken, from the outset, to the implications of the 2018 Decision and, consequently, to the extent of its duties under the Equality Act. In its 18 May 2022 letter (enclosed), in response to CLINUVEL's letter of 16 March 2022, NICE stated as follows under the heading "Post appeal actions":

> *"While the majority of appeal points were not upheld, the panel upheld 3 issues, namely:*
> - *That NICE had failed to include the IPPN at the 2nd committee meeting*
>   - *This point has now been addressed and the IPPN has been involved in the evaluation and has the same status as other consultees in this process.*
> - *That NICE did not demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act*
>   - *The appeal panel did not state that the committee breached the Equality Act as you incorrectly state in your letter – rather the appeal panel made it clear that NICE had not demonstrated adequate consideration of the legal duties and that although NICE's processes include an Equality Impact Assessment at each stage of the evaluation, this did not form part of the committee papers and therefore the appeal panel could not determine whether due consideration was given to the Equality Act. The appeal panel also suggested that the committee may want to seek further guidance on the relationship between the HST process and any specific need for reasonable adjustments with respect to the Equality Act. In response, the committee has considered this point with an open mind, and NICE drafted the stakeholder briefing note based on the committee's discussions which makes suggestions on how to address the evidence gaps by using the Decision Support Unit's technical support document.*
> - *That it was unreasonable for the committee to state that the evidence shows that the benefit of treatment with afamelanotide was small and not significant.*
>   - *In response the committee also considered this point with an open mind. In the post-appeal ECD, it states "the committee concluded that afamelanotide is effective and provides important benefits for patients, but further concluded that there are important uncertainties in the evidence and the size of the clinical benefits.""*
>
> *[emphasis added]*

2.4 As can be seen from the above:

2.4.1 NICE still did not, even in May 2022, accept that the Appeal Panel had found it to be in breach of its obligations under the Equality Act, even though the Committee had expressly admitted at the appeal hearing that it had not even considered EPP to be a disability (in part as it was not considered a "visible" disability by the Committee), let alone taken its anti-discrimination obligations into account. For the avoidance of all doubt, failures of this kind are themselves breaches of the Equality Act. CLINUVEL finds NICE's ongoing refusal to accept its responsibilities under the Equality Act to be remarkable.

2.4.2 Moreover, NICE appears to have arbitrarily limited the scope of its duties under the Equality Act in the future. NICE took the view that all that was required was: (i) consideration of the point "*with an open mind*" and (ii) exploring ways to address the "*evidence gaps*" required to implement its preferred economic model. As we explained in paragraphs 6.1-6.3 of our 24 March 2023 letter, if a provision, criterion or practice applied by NICE in its evaluation of highly specialised technologies put EPP patients at a disadvantage, then NICE was required not only to consider whether or not reasonable adjustments were required but actually to take reasonable steps to avoid the disadvantage. Such steps might, for example, entail a change of course away from the usual economic modelling approach and/or the usual thresholds applied to the resulting ICERs.

2.5 In short, a review of NICE's May 2022 letter and the FED indicates that the Committee (the membership of which was largely unchanged since the 2018 Decision) considered its pre-2018 approach did not give rise to any substantive breach of the Equality Act. For that reason, the Committee felt able largely to reapply the assessment procedures it had followed previously. No change of course in this regard was ever seriously contemplated. It is unsurprising, against that backdrop, that the Committee's approach was – once again – inconsistent with its obligations under the Equality Act.

2.6 The second matter is the Committee's approach to the various types of quantitative and qualitative evidence that were before it: the dismissal of the PASS, the other post-authorisation and observation studies and the treatment adherence data, on the one hand, and the imposition of further data generation requirements on CLINUVEL (namely, unvalidated vignette studies, in contrast to the findings of the European Medicines Agency), on the other. Further, there is no material discussion in the FED of the consideration of non-health factors and how these may have been taken into account by the Committee. Indeed it seems they were acknowledged but not seriously considered, nor given any weight in any discussion. Again, the unavoidable impression given to the reader of the FED is that the Committee never seriously contemplated departing from its pre-2018 approach. It never even asked itself, in the light of the unique difficulties posed by EPP as a condition and the value of the intervention with afamelanotide, whether a sufficient data pool already existed to approve afamelanotide's use in EPP in England (or might exist under an MAA). The very fact that (as you say in your letter) "*the Committee was not prepared to accept certain evidence that was presented to it*" demonstrates the fact that the Committee had already decided how it wanted to approach the evaluation of afamelanotide.

2.7 As such, contrary to your letter, we consider that the Committee would never have been prepared to change course in the light of the evidence presented to it.

3. Appeal point 1(b). NICE breached its duties under the Equality Act 2010

3.1 We are pleased that you agree with CLINUVEL that its appeal in relation to this ground should be referred to the Appeal Panel. However, we note that this is caveated by the words, "*so far as it relates to the duty to make reasonable adjustments*" and also your initial view that the Committee's failure expressly to address the need to promote equality of opportunity and its implications does not add to the substance of the argument.

3.2 We respectfully disagree. The Committee has an express statutory obligation to have regard to the need to advance equality of opportunity, as explained in paragraph 6.3.3 of our letter of 24 March 2023 (and as set out in terms in s. 149 of the Equality Act). This important consideration is one that the Committee should have borne in mind throughout the evaluation process, in particular when considering how to adjust its approach to the evaluation of highly specialised technologies. For example, in deciding whether a departure from its usual – but not mandatory – ceiling of a plausible ICER of £100,000 per QALY gained was appropriate, the Committee should have borne in mind that there is no alternative therapy for EPP patients in England and the significant impact of afamelanotide on the ability of EPP patients in England to participate in public life.

3.3 We would also add one final observation on your comments in points 1-7 of your letter. As you comment therein, CLINUVEL has identified certain disadvantages suffered by EPP patients and has advocated a more 'holistic' (ie, less ICER/QoL-focused) appraisal of afamelanotide. This is in line with the requirement in §43 of the HST Process Guide for appraisals to consider the "*overall magnitude of health benefits to patients*". As CLINUVEL has explained, if such an appraisal cannot be undertaken, the only remaining available method by which to avoid disadvantage to EPP patients is to 'flex' the normal ICER ceilings for recommending routine use, or managed access. (This is not only permitted under the HST Process Guide, as CLINUVEL pointed out in its Appeal point 2.2, but is also consistent with NICE's Guide to the methods of technology appraisal 2013 (the "**2013 Methods Guide**"), which explains in §6.3.1 that *"[t]he Appraisal Committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective or below which it would*," and also that "*consideration of the cost effectiveness of a technology is a necessary, but is not the sole, basis for decision-making*".) However, the duty to make reasonable adjustments is, of course, a duty that Parliament has imposed on NICE and not on CLINUVEL. It is NICE which should have taken steps to establish the nature of the disadvantage under which EPP patients are placed by virtue of its usual economic modelling approach, and it is NICE which should have considered what types of adjustment would have alleviated that disadvantage.

4. Appeal point 2.1: the recommendation is unreasonable in the light of the evidence submitted to NICE

4.1 CLINUVEL is grateful for the indication that the point raised in paragraph 9.7 of the 24 March 2023 letter will be referred to the Appeal Panel. CLINUVEL notes the scepticism expressed in your initial scrutiny letter as to whether the points raised in paragraphs 9.8 and 9.9 add anything substantive to the point raised in paragraph 9.7.

4.2 CLINUVEL considers that the reasonableness of the Committee's recommendation in terms of its compliance with NICE's Principles should be viewed in the round, i.e., in the light of all of the relevant matters set out in the NICE Principles and Constitution (and, indeed, the Committee's obligations under the relevant legislation, as well as the socio- and economic health outcomes of people living with EPP). As such, the matters raised in paragraphs 9.8 and 9.9 support the argument that NICE has failed to have regard to or deviated from the NICE Principles and so we do not consider that the referral in respect of paragraphs 9.8 and 9.9 in addition to paragraph 9.7 should be controversial.

4.3 That having been said, CLINUVEL acknowledges that the points raised in paragraphs 9.7-9.9 of its 24 March 2023 letter are inter-related: the considerations raised in paragraphs 9.8 and 9.9 (best value for taxpayers, fair use of resources and overall population need in circumstances where there is no other available treatment and afamelanotide is potentially life-changing) are specific examples of the factors that should (*per* paragraph 9.7) have been properly considered by the Committee as part of a broad balancing exercise but did not receive adequate regard. In the circumstances, CLINUVEL will pursue these as points as aspects of its point under paragraph 9.7.

5. Appeal points 2.5 and 2.6: the failure to place any (or any adequate) weight on treatment adherence data and data from post-authorisation and observational studies was irrational

5.1 CLINUVEL remains of the view that these failings are important both in their own right and taken collectively (together with Appeal point 2.4, in particular). They reflect the illogical way in which the Committee prioritised certain types of evidence over others. NICE, and the Committee, made multiple, inter-related errors, both in their approach to the decision-making process and in the extent to which they gave meaningful weight to particular types of evidence. The effect was to render the FED unreasonable.

5.2 Moreover, as regards Appeal point 2.5 specifically, we respectfully disagree that the fact that "*the Committee did take account of the fact that the adherence rate was high, whilst properly also*

acknowledging that adherence rates are not a direct marker of effectiveness and do not quantify the size of the treatment benefit" means that its approach was not irrational. As noted in paragraph 9.7 of our letter of 24 March 2023 (and indeed, as the Committee recognised in paragraph 4.42 of the FED), the Committee should have taken a broad range of considerations into account even if they could not 'feed into' an ICER calculation directly. The reality as regards treatment adherence data was that other than a brief mention in paragraph 4.27 of the FED (which did not even include any statement that the data would be taken into account), no further reference to it was made when the Committee set out its conclusions. The data, in effect, dropped out of the picture. As §6.1.9 of the 2013 Methods Guide indicates, taking account of a fact entails more than just referring to it in the 'Considerations' section of guidance: the reasoning for the Committee's conclusion should be explained "*with reference to the factors that have been taken into account*."

5.3 For the reasons set out above, CLINUVEL maintains its request for Appeal points 2.5 and 2.6 to be referred to the Appeal Panel in their own right. CLINUVEL understands from your comment at the end of Appeal point 2.6 (namely, that it does not appear to add anything of substance to the consideration required to resolve Appeal point 2.4) that you are content for the Appeal Panel to have regard to the way in which the Committee treated types of evidence other than vignette studies in assessing the rationality of its approach. If this understanding is correct, CLINUVEL considers that the points that it would have wished to make under Appeal points 2.5 and 2.6 can alternatively be incorporated into its submissions under Appeal point 2.4.

6. **Conclusion**

6.1 For all the reasons set out above, CLINUVEL requests that those grounds set out above are also referred to the Appeal Panel for determination. CLINUVEL otherwise reserves its rights.

Yours faithfully

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[redacted]

18 May 2022

Dear Mr [redacted]

Thank you for your letter dated 16 March 2022. Please accept my apologies for the delay in responding.

As you are aware, following the delays caused by the COVID-19 pandemic, NICE recommenced the evaluation of afamelanotide at the end of 2021. This included a stakeholder engagement meeting which we had hoped would take place in person, but for which circumstances necessitated taking place over video conference on 8 February 2022. The purpose of the engagement meeting was to re-establish communication with stakeholders and explain what the next steps for the topic would be including the re-launch of the consultation. Following this engagement meeting, we reconsulted on the ECD which was released following the third evaluation committee meeting which took place in March 2019. We also issued alongside the ECD the Decision Support Unit Technical Support Document on measuring and valuing health-related quality of life when EQ-5D data is not available and a stakeholder briefing note which outlined the next steps to be taken in the evaluation.

Post appeal actions

The third committee meeting took place after an appeal of the original FED which was issued in February 2018. While the majority of appeal points were not upheld, the panel upheld 3 issues, namely:

- That NICE had failed to include the IPPN at the 2nd committee meeting
    - This point has now been addressed and the IPPN has been involved in the evaluation and has the same status as other consultees in this process.
- That NICE did not demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act
    - The appeal panel did not state that the committee breached the Equality Act as you incorrectly state in your letter – rather the appeal

panel made it clear that NICE had not *demonstrated* adequate consideration of the legal duties and that although NICE's processes include an Equality Impact Assessment at each stage of the evaluation, this did not form part of the committee papers and therefore the appeal panel could not determine whether due consideration was given to the Equality Act. The appeal panel also suggested that the committee may want to seek further guidance on the relationship between the HST process and any specific need for reasonable adjustments with respect to the Equality Act. In response, the committee has considered this point with an open mind, and NICE drafted the stakeholder briefing note based on the committee's discussions which makes suggestions on how to address the evidence gaps by using the Decision Support Unit's technical support document.

- That it was unreasonable for the committee to state that the evidence shows that the benefit of treatment with afamelanotide was small and not significant.
    - In response the committee also considered this point with an open mind. In the post-appeal ECD, it states "the committee concluded that afamelanotide is effective and provides important benefits for patients, but further concluded that there are important uncertainties in the evidence and the size of the clinical benefits."

Each of these upheld appeal points has been addressed in the ECD released in March 2019, and reissued in March 2022, and NICE provided the company and stakeholders with advice for generating quality of life evidence using vignettes which the committee could consider. We built into the timelines the capacity for this evidence to be generated. We understand that you have decided not to provide any additional evidence for the upcoming committee meeting nor have you engaged in any constructive discussions to progress this topic, which is unfortunate. We do know that other stakeholders are keen to provide additional evidence for this evaluation and the next committee meeting.

Following reconsultation of the ECD and associated documentation, the HST team has been in touch with your company on several occasions (7 March 2022 and 17 March 2022) asking for you to provide access to the health economic model which can be shared with the consultees, who have requested it, given their willingness to provide additional evidence. This is a standard part of our process and stakeholders who request to model are bound by NICE confidentiality agreements. As yet, we have not had a response from you, [redacted]

Once you provide us with the requisite response, we will be able to release the model to the consultees and allow them to continue contributing to the evaluation.

Please note that NICE could be challenged that confidential information it has received should be publicly released in the interests of fairness during an evaluation, at appeal or resolution, through judicial review or otherwise. If this happens then data

owners must, on request, promptly reconsider whether it is necessary to maintain confidentiality. If disclosure is not possible, the data owner must be prepared to assert publicly that the information is confidential and must submit evidence justifying why NICE should maintain that confidentiality. Without such assertion and evidence, NICE is entitled to conclude that the information is no longer confidential. Please refer to section 3.1.22 of NICE's guide to the processes of technology appraisal for more information.

Stakeholder workshop

As previously mentioned, the stakeholder workshop which took place in February 2022 was meant to take place earlier, as was indicated during the meeting. It was unavoidably delayed due to the COVID-19 pandemic. Your characterisation of the meeting is at odds with the feedback we received from other attendees including EPP patients with whom NICE has continued to engage following the workshop. NICE has met with patient representatives to discuss the minutes of the committee meeting, to explain NICE's approach to evaluation of new medicines compared to other countries and to provide advice on new evidence that the patient representatives are putting together to aid the committee in their considerations. We have established a constructive dialogue underpinned by respect and collaboration.

SMC Ultra-orphan medicines pathway

The EPP patients involved in this evaluation queried at the workshop in February 2022 why NICE could not take the approach Scotland has taken. As mentioned above, NICE has its own methods and processes which differ from Scotland. Scotland as a devolved nation develops its own evaluations on whether new treatments can be considered clinically and cost-effective within the NHS in Scotland.

According to the SMC website, afamelanotide has been conditionally approved for three years at the end of which, the SMC will review the evidence to make a final decision on its routine use in NHS Scotland. There are 4 conditions that *must* be met for an ultra-orphan medicine to be available through the pathway. These include that the company:

- has the medicine validated as an ultra-orphan according to the SMC definition
- makes a full submission to the SMC for the initial assessment stage that meets SMC requirements for assessment under the ultra-orphan process
- offers a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment Group (PASAG)
- supports the data collection arrangements that meets the evidence generation requirements for assessment under the ultra-orphan pathway

(hiips://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/)

Afamelanotide has been included in the SMC's ultra-orphan medicines risk share scheme (hiips://www.nss.nhs.scot/specialist-healthcare/financial-risk-share/ultra-orphan-medicines). Therefore, the 4 conditions above must have been met.

This publicly available information was made available to the EPP patients who made the query.

NICE's role and Clinuvel's approach

One of NICE's main remits is to ensure that clinically and cost-effective health technologies are made available to patients and their families within the NHS in England. NICE's Highly Specialised Technologies programme has a track record that speaks for itself with over 90% of treatments having been recommended for use within the NHS.

Clinuvel's approach to pricing is unique and the choice to treat all life-sciences ecosystems as monolithic is your prerogative. Equally, NICE's constitution and functions are clearly laid out in legislation and it has well-established methods and processes to establish both clinical effectiveness and value for money for the NHS that it follows for the evaluation of new treatments (upon which it has consulted with stakeholders).

Beyond July 2022 Committee meeting

In terms of next steps, if the committee decide on a final evaluation determination following the next meeting in July 2022, all consultees will be entitled to issue a fresh appeal of that determination. Judicial review is a remedy of last resort and therefore will not be available until appeals have been exhausted.

According to the guide to NICE's appeal process, after an appeal has been upheld and final draft guidance returned to the advisory committee:

> "The technology will be returned to the relevant programme and work will start on reviewing the guidance as advised by the Appeal Panel and agreed by the NICE Guidance Executive.
>
> The advisory committee will meet to consider the Appeal Panel's decision for review. The advisory committee will then produce revised final draft guidance. When the final draft guidance is produced, it will be distributed to consultees and commentators. Consultees will then have a further opportunity to appeal or to identify any factual errors.
>
> If an appellant from the first appeal lodges another appeal, the appeal letter must not raise the same points presented in the first appeal or those points

presented by another appellant at the first appeal hearing. The Appeal Panel will have already determined the outcome on these points."

In summary, NICE has taken the upheld appeal points back to the committee, which it considered fully with an open mind and responded to those points. The committee's considerations are detailed in the ECD issued after the third committee meeting. In this exceptional circumstance, due to the delay caused by COVID, we held a workshop to re-engage with stakeholders and have re-issued the ECD to allow stakeholders an opportunity to re-comment on the committee's conclusions, along with supporting information relevant to the conclusions. This was to enable the other stakeholders, who are keen to provide additional evidence for this evaluation, with as much information as possible to respond to committee's considerations.

We have always entered discussions with Clinuvel in an open and constructive manner, and with the intention of trying to identify ways in which the company could support the evaluation; ensuring fair consideration of this treatment for patients with EPP in accordance with our methods; that is, accounting for both clinical effectiveness and value for money for the NHS. As always, we remain open to discussions with the company on this topic in advance of the committee meeting in July 2022.

Alternatively, if Clinuvel is no longer willing to take part or engage in this evaluation, it can consider withdrawing its submission from the process. However, this approach would result in NICE terminating the evaluation and issuing guidance that states we are unable to make a recommendation for afamelanotide. We would stand ready to re-start a new evaluation should the company wish to pursue this in the future.

Yours sincerely,

Helen Knight

Acting Interim Director of Medicines Evaluation, CHTE

National Institute for Health and Care Excellence