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

Dear Dr Chakravarty,

1. INTRODUCTION

1.1 We refer to the Final Evaluation Document dated 13 March 2023 ("the **FED**") provided by the National Institute for Health and Care Excellence ("**NICE**") to CLINUVEL in relation to one of the Company's products, afamelanotide. A copy of the FED was published on the NICE website on 13 March 2023.

1.2 The FED records the evaluation of the product conducted by NICE's Highly Specialised Technology and Evaluations Committee and states that afamelanotide is not recommended, within its marketing authorisation, for preventing phototoxicity in adults with erythropoietic protoporphyria ("**EPP**"). As a consequence, afamelanotide will not be nationally commissioned by the National Health Service ("**NHS**") England.

1.3 CLINUVEL UK Limited ("**CLINUVEL**", "**the Company**") appeals the FED and the failure by NICE to recommend afamelanotide on the basis that (i) NICE failed to act fairly in the exercise of its discretion and/or acted in excess of its powers; and (ii) the conclusions in the FED are unreasonable in light of the evidence submitted to NICE. These grounds are developed below.

1.4 This is the second time that CLINUVEL has had to bring an appeal against the decisions and decision-making process of the Highly Specialised Technologies Committee ("the **Committee**"), which continues to deny EPP patients in England access to the only approved treatment for their condition. CLINUVEL is disappointed to find itself in this position again. The position is particularly regrettable because some of the same errors that the Appeal Panel identified in October 2018 (the "**2018 Decision**") as vitiating the previous Final Evaluation Document, are repeated. CLINUVEL also considers that the length of time that it has taken to reach this point is extraordinary and not justified. CLINUVEL also has concerns about the transparency and fairness of the decision-making process that has led to this outcome. While CLINUVEL has not, to date, had the opportunity to challenge NICE's decisions to an independent, external body, it fears that such a challenge may ultimately be the only way in which the evidence in relation to afamelanotide can receive the fair, transparent and effective consideration that both the Company and, most importantly, EPP patients in England, deserve.

1.5 We respectfully request an oral hearing in this case.

2. THE CONDITION: ERYTHROPOIETIC PROTOPORPHYRIA ("EPP")

2.1 EPP is a very rare inherited metabolic disorder leading to a deficiency of the enzyme ferrochelatase. The reduced activity of this enzyme causes phototoxicity when patients are exposed to specific wavelengths of visible light (including sunlight and artificial light). Exposure to light leads to anaphylactoid reactions, incapacitating phototoxicity, which may involve redness and swelling of the skin. Abnormally high levels of protoporphyrin IX can also cause liver disease.

2.2 The disorder usually presents in childhood with the most common symptom being acute phototoxicity. It affects areas exposed to visible light and tends to be intractable. A few minutes of exposure to the sun/light induces pruritus, erythema, swelling and "pain". Longer periods of exposure may induce second degree burns. After repetitive exposure, patients may present with lichenification, hypopigmentation, hyperpigmentation, and scarring of the skin. As EPP reactions can last days to weeks, EPP patients are unable to lead normal lives owing to their inability to spend time outdoors and/or be exposed to artificial light sources. EPP is a lifelong condition. It is also incurable. It has a profound impact on patients, who develop conditioned behaviour leading to isolation and a lack of social interaction.

3. THE PRODUCT: SCENESSE® (AFAMELANOTIDE 16MG)

3.1 CLINUVEL's product, SCENESSE®, is an injectable 16mg implant formulation of the novel drug afamelanotide used to treat patients with EPP. It is the only product authorised for the prevention of phototoxicity in EPP patients anywhere in the world. SCENESSE® is used to help prevent or reduce the phototoxic reactions patients experience so that these patients can lead more normal lives.

3.2 EPP affects between 1 in 75,000 – 1 in 200,000 people[1]. An estimated 400 EPP patients would benefit from SCENESSE® treatment in England. Because the number of patients with EPP is low, the disease is considered 'rare', and SCENESSE® was designated an 'orphan medicine' (a medicine used in rare diseases) by the European Medicines Authority ("**EMA**") on 8 May 2008.

3.3 SCENESSE® is an implant which is injected subcutaneously once every 2 months. It has been shown in clinical studies to provide photoprotection, increasing the amount of time patients can spend in sunlight (which is a proxy measure for all light exposure), with no or reduced phototoxicity, and to improve patients' quality of life. In the CUV039 study, involving 93 patients with EPP, patients were treated with either SCENESSE® or a placebo (a dummy treatment) over a six-month period. Daily records of exposure to sunlight between 10 am and 6 pm showed that patients treated with SCENESSE® spent on average 115.6 hours in direct sunlight without experiencing pain during the six-month period compared with 60.6 hours for patients treated with placebo.

3.4 Data from observational and post-authorisation use of SCENESSE® – including long-term use and post-authorisation safety studies – demonstrate the impact and effectiveness of treatment for EPP patients. This includes an increased ability for patients to expose to sun and light, reduced and less severe phototoxicity, improved patient quality of life, positive impact on liver function, and a rate of year-on-year treatment adherence above 90%. These data have provided to the Committee during the NICE review process, with many subject to peer-review prior to publication.

4. APPROVALS BY THE EMA & OTHER REGULATORS

4.1 The EMA granted an EU centralised marketing authorisation for SCENESSE® in 2014. The EMA's European Public Assessment Report ("**EPAR**") Summary for the public states:

"*… Scenesse's benefits are greater than its risks and recommended that it be given marketing authorisation. The CHMP noted that Scenesse led to an increase in the amount of time patients could spend in direct sunlight without experiencing pain. Although the additional time spent in sunlight was small, the*

[1] Source, Orphanet, accessed 18 March 2023.

Committee considered the possible improvements in quality of life, the unmet medical need in patients with EPP, and the mild side effects seen during short-term treatment with the medicine in deciding to recommend approval for Scenesse in the EU. The Committee also consulted individual patients and experts on their experience with Scenesse." (Emphasis added)

4.2 SCENESSE® has been authorised in Europe under 'exceptional circumstances' on the basis that it has not been possible to obtain complete information about the benefits of SCENESSE®, in part due to the unique nature of EPP. In approving SCENESSE®, the EMA recognised the complexity of the disorder and that the specificity of the condition made it impossible for the Company to provide the usual comprehensive clinical trial data that would ordinarily be required to demonstrate the extent of efficacy of the product. Instead, the EMA relied both on the statistical evidence of photoprotection and on additional evidence, including the testimony of patients and expert clinicians in the European Union. SCENESSE® can only be made available to EPP patients under a controlled distribution programme in line with the approved risk management plan as agreed with the EMA. SCENESSE® has been re-assessed by CHMP on an annual basis since its authorisation in 2014 and has also regularly been assessed by PRAC following periodic safety updates[2]. On each occasion the decision has been to maintain the marketing authorisation. Following the UK's decision to leave the European Union, the SCENESSE® marketing authorisation was "grandfathered" into a UK marketing authorisation under exceptional circumstances.

4.3 In February 2021, the Scottish NHS made SCENESSE® available in Scotland via the Ultra-Orphan Medicines Pathway. [redacted]

4.4 SCENESSE® is also now accepted as standard of care for EPP across a number of European countries. CLINUVEL has established a uniform price for the product, treating all payors transparently and equally, recognising the unique challenges of providing treatment to EPP patients.

4.5 Finally, SCENESSE® was approved by the US Food and Drug Administration in 2019 and is now covered by over 100 US insurers. In 2021 the product was added to the Israeli National Health Basket for EPP.

4.6 The unavoidable conclusion is that the continued non-availability of SCENESSE® to patients on the NHS in England is an outlier. That position has profound consequences for the quality of life of EPP patients.

4.7 CLINUVEL was, and remains, willing to enter into commercial discussions and negotiation with NHS England with a view to concluding a managed access agreement ("**MAA**") to minimise the financial risk and budget impact to the NHS associated with commissioning the product.

5. SUMMARY OF CLINUVEL'S APPEAL

5.1 This appeal is brought for the following four, overarching reasons:

5.1.1 *First*, NICE has breached its duties under the Equality Act 2010 ("**Equality Act**"). This falls within **ground 1(b)** of the grounds under which one can appeal final draft guidance under the Highly Specialised Technologies ("**HST**") programme.

5.1.2 *Second*, the procedure by which the Committee reached the FED did not comply with the requirements of fair consultation. This falls within **ground 1(a)**.

[2] See SCENESSE® EPAR, Procedural steps taken after authorisation: SCENESSE® INN-Afamelanotide (europa.eu), accessed 19 March 2023.

5.1.3 *Third*, the fairness of the Committee's decision-making process and the rights of CLINUVEL were further undermined by reason of delay. This falls within **ground 1(a)**.

5.1.4 *Fourth*, the FED is irrational in multiple respects. It is illogical/inadequately reasoned; it fails to follow relevant NICE guidance; and its statements of fact and appraisal of the evidence contain material flaws. This falls within **ground 2** of the grounds under which an appeal can be lodged, in that it rendered the FED unreasonable in the light of the evidence.

5.2 These four reasons are addressed in turn below, with the separate points enumerated in accordance with the relevant NICE grounds of appeal. The four reasons overlap to at least some extent: for example, certain irrationalities highlighted under **ground 2** also gave rise to procedural unfairness in that they compromised the ability of CLINUVEL properly to present its submissions and evidence in favour of the recommendation of afamelanotide and so also fall under **ground 1(a)**. For clarity and concision, CLINUVEL does not repeat points that are already explained under another ground.

6. NICE HAS BREACHED ITS DUTIES UNDER THE EQUALITY ACT [Ground 1(b)]

The statutory context and the 2018 Decision

6.1 Under sections 29(6) and 29(7)(b) of the Equality Act, a person exercising a public function (i) is required not to "*do anything that constitutes discrimination, harassment or victimisation*"; and (ii) is under a duty to make reasonable adjustments. The duty to make reasonable adjustments includes "*a requirement, where a provision, criterion or practice … puts a disabled person at a substantial disadvantage in relation to a relevant matter in comparison with persons who are not disabled, to take such steps as it is reasonable to have to take to avoid the disadvantage*".[3] Failure to comply with this obligation amounts to unlawful discrimination, for the purposes of the Equality Act[4].

6.2 A public authority is also required in the exercise of its functions to have due regard to *inter alia* the need to eliminate discrimination and the need to "*advance equality of opportunity between persons who share a relevant protected characteristic and persons who do not share it*",[5] disability being one of the protected characteristics. A failure to have such due regard is a further and separate breach of the obligations imposed on a public authority by the Equality Act.

6.3 NICE is a public authority exercising a public function; EPP is a disability under the Equality Act; and the phrase "*provision, criterion or practice*" is to be construed widely to include, for example, policies, rules or practices. Thus, NICE was under a duty:

6.3.1 to consider whether its approach to the evaluation of highly specialised technologies, as reflected in the 'Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes' (the "**HST Process Guide**"), placed EPP patients at a substantial disadvantage;

6.3.2 if so, to take reasonable steps to avoid that disadvantage; and

6.3.3 to have regard to the need to avoid discrimination against EPP patients and to advance equality of opportunity.

6.4 The Appeal Panel found in the 2018 Decision that these requirements had not been complied with (to the extent that it was even possible to assess the consideration that the Committee had made of its duties under the Equality Act). See §§54-55, which read in material part as follows:

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[3] Equality Act 2010, s 20(3). For completeness, "*substantial*" is defined in section 212 as "*more than minor or trivial*".
[4] Equality Act 2010, s.21.
[5] Equality Act 2010, s.149(1). Further clarification as to the content of the duty of due regard to the need to advance equality of opportunity is set out in s.149(3).

"[I]n this case, the panel were not able to consider the Equalities Impact Assessment said to have been completed by NICE as this had not been published and was not available to either the appellants or the panel. The panel could not see evidence of consideration of NICE's duties under the Act with respect to the use of afamelanotide in EPP specifically, elsewhere in the documents provided. Furthermore, the evaluation committee confirmed during the hearing that they had not taken into account any anti-discrimination legislation in reaching their decision. Irrespective of whether ICERs were indeed determinative of the committee's decision, or whether the use of ICERs in this way would constitute a discriminatory "provision, criterion or practice", the panel therefore concluded that NICE had not demonstrated adequate consideration of the legal obligations placed on it as a public authority.

[…] The appeal panel suggests that the Committee may wish to seek further guidance from the Institute, if the Committee considers that it is required, on the relationship between the HST Process Guide and any specific need for reasonable adjustment(s) in relation to a particular cohort of people sharing a protected characteristic."

6.5 It is plain from the 2018 Decision – in particular, the absence of any evidence of compliance with the duty of due regard (see above) and the Committee's failure even to appreciate that EPP is a disability (see §51), let alone consider reasonable adjustments – that, contrary to what was suggested by NICE to CLINUVEL in a letter dated 18 May 2022 (attached), the Appeal Panel found the Committee not to have complied with its obligations under the Equality Act.

The Committee's recognition of the need to adjust its approach

6.6 The first stage of the three-part test set out above is not in dispute. The FED recognises in section 4.8 that EPP patients are placed at a substantial disadvantage by the HST Guidelines because of "*the specific challenge in measuring the effect of the condition and its treatment on quality of life*" and that the ingrained, conditioned behaviours of EPP patients in terms of avoiding light exposure further compound the difficulties of quantifying treatment effects. The Committee thus recognised that: EPP is a disability, for the purposes of the Equality Act, and that the application of its usual methodologies and approach to assessment would place EPP patients at a substantial disadvantage, such that a reasonable adjustment was required.

6.7 However, at no point does the FED identify, either at all or with sufficient precision, what reasonable adjustment it has made to its approach. In order to satisfy the obligations set out in the Equality Act it will ordinarily be necessary to: (i) identify the nature of the disadvantage that follows from the provision, criterion or practice; (ii) identify the reasonable adjustment that has been made in light of that disadvantage; and (iii) explain why that adjustment is 'reasonable' (in the sense that, to put it broadly, it is a practicable and proportionate means of addressing the disadvantage). An adequate explanation of the approach taken may well also involve identifying why other potential adjustments have been rejected as (for example) not suitable to meet the disadvantage or not proportionate. Each of these elements forms part of the lawful discharge of the Committee's obligations. The FED does not come close to articulating this analysis. Instead, it is said in section 4.8:

"*The committee concluded that it would take into account the nature of EPP as a disability throughout its decision making, and how it would be appropriate to adjust its approach in the context of this disability.*"

To the extent that this reasoning can be understood, it appears to be that the nature of EPP as a disability was taken into account throughout but without identifying any specific change or adjustment that should be made.

The inadequate nature of the adjustment

6.8 A sympathetic reading of the FED suggests that there was just one aspect of its approach to which the Committee was prepared to contemplate adjustments: its economic model for quantifying the quality of life ("**QoL**") benefits of afamelanotide. This is plain from the specific passages in which potential

adjustments were discussed: sections 4.22 and 4.50 concerning QoL evidence submitted by the International Porphyria Patient Network ("**IPPN**") from two studies; sections 4.51 and 4.53 setting out the incremental cost-effectiveness ratios ("**ICERs**") derived from this evidence and expressing the view that the use of these ICERs comprised "*a part of a reasonable adjustment given the nature of the condition*"; the discussion in sections 4.45 about whether to apply quality-adjusted life year ("**QALY**") weighting; and the reference in section 4.47, in the context of a discussion of the quantification of treatment benefits, about the reasonableness of "*consider[ing] alternative methods to capture the benefits of afamelanotide*".

6.9 In short, to the extent that the FED sets out the Committee's reasoning in relation to this issue at all, the Committee concluded that NICE could discharge its obligations to make reasonable adjustments, under the Equality Act, by focussing on the evaluation and quantification of QoL. The question of whether such an approach would be sufficient to fulfil the obligations under the Equality Act, and what reasonable adjustments were required to the Committee's usual approach, was viewed through a narrow, QALY-focused prism. This gave rise to three serious and fundamental flaws:

(1) The ICERs were, again, determinative

6.9.1 While the Committee stated in section 4.42 of the FED that "*the ICER was not the only contributor to its view on value for money*," it is clear from section 4.53 that, once again, the ICERs – and, by extension, the quantitative QoL data from which they were derived – essentially drove the decision not to recommend afamelanotide for routine use.

6.9.2 The ICERs also determined the Committee's decision not to recommend afamelanotide for a managed access agreement ("**MAA**"). The Committee, having concluded (see section 4.54) that the appropriate pathway to market access was through the Innovative Medicines Fund ("**IMF**").[6] went on to conclude in section 4.57 that because "*[t]he most optimistic potentially plausible ICER … remained in excess of £100,000 per QALY gained*," afamelanotide could not be considered for managed access.

(2) There was no rigorous, comprehensive consideration of the impact of the disadvantages suffered by EPP patients

6.9.3 While the Committee noted the multiple and significant health and non-health impacts of EPP in the introductory part of its consideration of the evidence (see FED sections 4.1 to 4.4), there is no evidence in the FED that the impact of the unique disability posed by EPP on the "*overall magnitude of health benefits to patients*" (HST Process Guide, §43) or on non-health benefits actually played any material role in the analysis that led the Committee to reach its final decision as to whether to recommend afamelanotide.

6.9.4 Only after the Committee had <u>already</u> reached its negative conclusion on cost-effectiveness and managed access did it discuss, in sections 4.58-59 of the FED, whether there were other factors that necessitated further adjustments. The conclusion of that discussion, which was brief and at a high level of generality, was that such factors had "*already been taken into account*" such that no further adjustments were needed to the Committee's approach. Again, this approach was not consistent with the Committee's obligations under the Equality Act.

6.9.5 No specific consideration was given to whether reasonable adjustments were required in view of (for example): the extent to which clinical trial data may underestimate the impact of the disorder; the lifelong conditioned behaviour of EPP patients to avoid light exposure and phototoxicity; the impact of prodromal symptoms; the impact of cumulative exposure; EPP

[6] This was despite the rules of the IMF – under which no product has been successfully reimbursed to date – requiring an ICER <£100,000. The Committee was aware, when it proposed the IMF pathway, that the IMF would apply the same ICER-driven threshold. It was plain, therefore, that NHS England would not engage with commercial proposals that did not meet precisely the same threshold as that adopted by the Committee (indeed this transpired to be the case, notwithstanding CLINUVEL's innovative approach to attempt to arrive at a suitable commercial proposal).

patients' anxiety towards light exposure; the impact of the disorder on employment, study or family life; the impact of the disorder on interpretation of clinical and/or observational trial results; the rarity of the condition, even by the standard of HST appraisals; the impact of EPP patients' diagnostic odyssey; the challenges of conducting clinical trials and developing clinical assessment tools for a previously unaddressed disorder; the proposed use of a preventative therapy in the disorder, rather than one which focused on symptomatic relief; the lack of alternative therapy; and the unique nature of the findings of the EMA in its review and approval of SCENESSE® under exceptional circumstances. There was no discussion of whether such factors – individually and/or collectively – warranted the adoption of a different approach. In particular, the Committee did not consider whether a more holistic approach to the appraisal of afamelanotide, taking into account at least the matters outlined above, was required in order to address the disadvantages suffered by EPP patients.

(3) The right questions were not addressed

6.9.6 As noted above, NICE's duty under the Equality Act was to take reasonable steps to "*avoid the disadvantage*" to EPP patients to which its usual appraisals processes (including economic modelling and centrality of the resulting ICERs) would otherwise give rise. Nowhere in the FED – including the critical sections on cost-effectiveness, managed access and other factors – is there any consideration of the 'exam question' under the Equality Act, which is whether the adjustments the Committee made were sufficient to avoid disadvantage to EPP patients in view of EPP's unique and debilitating difficulties.

6.9.7 Similarly, there is no discussion of the need to promote equality of opportunity and its implications for adjustments to the Committee's approach.

6.10 The closest that one gets to an explanation in the FED of why the Committee did not consider any more significant deviation from its usual approach to be required are:

6.10.1 section 4.8, in which the FED states that the challenges of measuring treatment effect are "*not unique to EPP*" and, thus, that the Committee "*should not deviate entirely from its normal approach*"; and

6.10.2 sections 4.42-43 of the FED, which indicate that the Committee considered that a more peripheral role for ICERs in the value for money assessment – or even a willingness to depart materially from the threshold of a most plausible ICER of £100,000 per QALY gained without the relevant criteria for QALY weighting being met (per HST Guidelines, §§50-54) – would be in tension with the NICE Principles and "*the crucial importance of considering value for money in a fair and consistent way*".

6.11 Starting with the latter of these, for the reasons discussed below, insofar as the Committee concluded that the NICE Principles and/or HST Process Guide mandate a central role for ICERs in the assessment of value for money (especially where the comparison is to an alternative of no treatment at all) or an ICER below £100,000/QALY, the Committee was wrong. There is no need for such a prescriptive, rigid approach.

6.12 As for whether the measurement-related challenges posed by EPP are unique, the Committee's view is unsustainable in light of the evidence and material submitted, including by the patient interest groups. NICE provided no evidence in the FED that the challenges seen in other HST appraisals are relevant, or equivalent, to those seen in this review. Conversely, CLINUVEL and other stakeholders presented extensive evidence during the review clearly demonstrating the unique nature of: (i) EPP as a disorder

and (ii) the (largely invisible) disability to EPP patients[7] - and the consequent unique inability to generate quantitative QoL evidence to fit NICE's preferred models. This included:

6.12.1 noting the findings of the EMA in 2014[8] that:

> "*Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin. It is also conceivable that the complexity of the EPP patients* (sic) *behaviour and the dependence of phototoxicity with environmental factors in real life differ to such an extent that the actual benefit cannot be captured in conventional clinical trial designs, for ex. randomised blinded clinical trial design and that no design could address this matter taking into account the current scientific and technical knowledge*."
>
> To CLINUVEL's knowledge, as conveyed to the Committee, no other indication has been recognised by the EMA prior to, or since in such a manner. CLINUVEL accepts that the EMA findings above are in the context of an assessment procedure for a marketing authorisation that assesses the benefit-risk balance of permitting a particular product to be sold as a medicine. However, they go to the heart of the nature of EPP – and why a traditional, rigid and ICER- only based analysis of the benefits of SCENESSE® is not possible;

6.12.2 outlining the unique characteristics of EPP which are not seen in any other disorder, including those which lead to a lifelong conditioned behaviour of light avoidance. These include the nature of phototoxicity (a lifelong acute reaction triggered by cumulative exposure to light), the impact of invisible reactions, prodromal symptoms, and anxiety towards light exposure; and

6.12.3 noting the lack of indications or comparable disorders which exist or have been presented for NICE review previously. (The Committee and evidence review group ("**ERG**") were both critical of CLINUVEL's choice of reference disorders when building its economic modelling; notably, though, neither has identified any other disorders which better reflected the nature of the disease, with the ERG presenting one of the same disorders in its modelling response.)

6.13 Critically, the findings of the EMA are not limited to the impact of EPP on patients' QoL or to the ability to "*generate data on efficacy and clinical benefit of EPP treatment*" as summarised in the FED (section 4.8). Rather, the EMA's findings extend to other measures of overall disease impact and clinical effectiveness, such as a patient's ability to expose themselves to light without phototoxicity or with reduced phototoxicity, behavioural changes, or even more recent findings on the impact of treatment on patients' sleep patterns or liver function.

6.14 In any event, the onus is not on CLINUVEL to demonstrate that EPP is unique (though the Committee placed that precise burden on CLINUVEL during Committee Meetings by requiring it to show why EPP was "*unique*"). To reiterate the points above, the burden lies on NICE to make such adjustments to its approach as are needed to prevent EPP patients from being significantly disadvantaged in the appraisal process compared to any other group. As outlined above, the Committee made just one adjustment to its model, before concluding that all relevant factors had been taken into account and that no further adjustments were needed. But this adjustment is neither reasonable nor adequate. It does not purport to be a reasonable adjustment, that takes into account in a meaningful or comprehensive way, the unique features of EPP as a disability and the difficulties of not only QoL measurement but measurement of other aspects of the disorder; rather, it seeks to incorporate EQ-5D data to fit within NICE's pre-existing model.

[7] In this regard, it is telling that even the Committee in 2018, failed to recognise EPP as a disability by reason of its invisibility: see 2018 Decision, §51.
[8] Which the FED states (section 9.4) that it "*does not seek to re-examine*".

An appropriate reasonable adjustment

6.15 CLINUVEL submits that the fair and proportionate adjustment for the Committee to have made in all the circumstances – not least, the lack of any alternative treatment and the very long time for which EPP patients in England have already been waiting for NICE's processes to conclude – would have been to recognise that even above a "*most plausible ICER of £100,00 per QALY gained*" (per §50 of the HST Process Guide), afamelanotide could be acceptable as an effective use of NHS resources. This recommendation could have been for routine use or for managed access.

6.16 Without repeating submissions that are made under **ground 2** below, CLINUVEL emphasises two particular points in favour of such an adjustment being both appropriate and indeed what is required in the light of the particular nature of EPP (as a disability).

(1) The adjustment is modest and reasonable

6.17 As noted above (and discussed further below), the Committee accepted the evidence from the IPPN studies and used that evidence to generate associated ICERs ranging from £133,748 to £253,676 per QALY gained (FED, section 4.53). The Committee stated that it considered the figure of £133,748 to be "*a potentially plausible ICER*". It is important to note that this figure is itself somewhat inflated. As set out in several of the submissions made by CLINUVEL to the Committee, the ICER would be £121,233 at the uniform price that CLINUVEL has repeatedly offered. While the Committee qualified this by noting that £133,748 represented "*the most optimistic scenario*", on the other side of the coin it expressed concern that the ICERs generated by the original model and the ERG's exploratory base-case assumptions (ranging from £1.46 million to £1.89 million) might be overestimates if the QALY gains associated with afamelanotide were underestimated and, notably, the FED does not endorse one of the ICER estimates as a "*most plausible*" one over the others. The Appeal Panel should therefore proceed on the basis that £133,748 per QALY gained is no less plausible than any other of the various ICER estimates in the FED.

6.18 As is also discussed below:

6.18.1 £133,748 is outside the range that the HST Process Guide indicates will normally be accepted to be an effective use of NHS resources but by a modest amount (some £33,748). It is not orders of magnitude adrift.

6.18.2 Even without making any adjustment to the approach set out in the HST Process Guide, the Guide <u>already</u> recognises that it may be appropriate – in some cases – to recommend technologies for which the most plausible ICER exceeds £100,000 per QALY gained. The Guide does not impose any absolute bar.

6.18.3 The factors to which §55 of the HST Process Guide specifically direct attention, in such cases, include "*[w]hether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained*". For all the reasons already set out above, this factor clearly applies in the case of afamelanotide.

6.19 In the circumstances, the adjustment for which CLINUVEL advocates is far from a radical departure from the HST Process Guide; rather it is one that is already anticipated in the Guide. Indeed, as explained in §§9.12 below, CLINUVEL's position is that accepting ICERs outside the normal range is consistent with the NICE Principles and the Guide. NICE's failure accept an ICER that is outside the normal range – but not by orders of magnitude – in this case was <u>un</u>reasonable. It was a failure to make a reasonable adjustment and breach of NICE's obligations under the Equality Act.

(2) No other reasonable adjustment has been suggested that would avoid disadvantage to EPP patients

6.20 CLINUVEL has already explained above why the adjustment made by the Committee – namely, being willing to incorporate the IPPN-derived EQ-5D data into its model but not being willing to accept ICERs outside the normal range – does not address adequately the disadvantage that EPP patients face in the HST appraisals process. In short, any methodology that focuses on metrics derived from QoL-only data will understate the benefits of afamelanotide and will not take sufficient account of either the difficulties of measuring the positive and holistic impact of EPP or its clinical effectiveness. This was precisely the point identified and relied on by the EMA.

6.21 As is discussed further in §§9.20-9.25 below, the Committee's suggestion in the course of the appraisal process for afamelanotide that CLINUVEL could/should have prepared a 'vignette' study, comprising a qualitative questionnaire of patients that could have been used to inform the quantitative estimates of treatment effectiveness, was unreasonable.

6.22 While CLINUVEL notes that §41 of the HST Process Guide confers on the Committee "*the discretion to take account of the full range of clinical studies that have been carried out*" and requires it to "*consider all of the evidence presented to it*", in fact (as discussed in §§7.7 below) the Committee has expressed scepticism about the ability of the appraisal process to accommodate "unstructured" qualitative data. It has also (illogically, in CLINUVEL's submission) rejected and/or not given any material weight in its decision-making process to a range of other sources of evidence, including the treatment adherence data (discussed at §§9.26-9.29 below) and quantitative data from the post-authorisation and observational studies (discussed at §§9.30-9.31).

6.23 The Committee's own logic therefore boxes it into a corner where the only available method by which to address adequately the shortcomings of the ICER estimates is explicitly to acknowledge the need to 'flex' the normal range for recommending technologies. This is the reasonable adjustment that the Committee failed – unlawfully – to make.

Conclusion

6.24 Notwithstanding the findings of the Appeal Panel in the 2018 Decision, the Committee has followed the same rigid and predetermined approach in the FED. Lip service has been paid to NICE's equalities duties and to the unique difficulties associated with the appraisal of EPP and debilitating nature of EPP but in substance there has been no substantive adjustment to the appraisal methodology (as is required by the Equality Act).

6.25 The very language used on the first page of the FED – "*There is <u>some evidence</u> from clinical trials that afamelanotide provides benefits for people with EPP*" (emphasis added), with the unnecessary qualifier that implicitly diminishes the value of the data generated from clinical trials – sets the tone for the analysis that follows. It underlines that, in the Committee's view, there is still a firm hierarchy: any evidence that does not fit into its model, however weighty or compelling, cannot 'move the dial'. Such an approach is contrary to NICE's duties under the Equality Act; is discriminatory; and fails to demonstrate that NICE had due regard to the need to advance equality of opportunity.

7. THE PROCEDURE FOLLOWED BY THE COMMITTEE DID NOT COMPLY WITH THE REQUIREMENTS OF FAIR CONSULTATION [Ground 1(a).1-2]

The requirements of a fair consultation

7.1 It is well-established that any fair consultation process will (*R (ex parte Gunning) v London Borough of Brent*[9]):

7.1.1 be conducted at a time when proposals are still at a formative stage;

[9] [1985] 4 WLUK 200.

7.1.2 provide sufficient information to consultees to enable them to make an informed response;

7.1.3 provide sufficient time for consideration and response; and

7.1.4 involve the decision-maker conscientiously taking account of submissions made to it.

7.2 For the reasons set out below, the process adopted by the Committee did not meet these requirements.

The procedure followed by the Committee was not sufficiently transparent [ground 1(a).1]

The Committee's stated approach to qualitative data as of February 2022

7.3 In its draft evaluation consultation document ("**ECD**") that was shared with stakeholders in February 2022, the Committee explained its view as to the utility and role of qualitative evidence as follows, in sections 4.20-21:

"*… The committee agreed that qualitative evidence collected systematically and analysed using standard qualitative techniques could potentially have provided more scientifically robust information on the full breadth of patient experiences. It recognised that, in that sense, the qualitative information it had been presented with had some limitations. However, it concluded that it was highly valuable in informing the nature of the condition, the benefits of the treatment and the meaning of those benefits for people with the condition and their families. Given the challenges associated with EPP, the committee concluded that it was important to take into account patient testimonies and other qualitative evidence as part of its decision making.*

Nevertheless, the committee explained that qualitative evidence, even when formally analysed, could not be directly used in quantitative analyses or to quantify the size of the treatment benefits. The committee also noted that such evidence could not be directly used in an economic analysis. It noted that it was important to consider how the benefits of afamelanotide could be quantified as part of its decision making." (Emphasis added)

7.4 In short, the Committee takes the position that, while highly valuable and insightful, qualitative evidence could not inform the quantitative modelling (which, as discussed above, was to the beginning of the end of the Committee's analysis). This view was identical to that which had been expressed to stakeholders in a previous draft ECD in February 2020.

7.5 Meanwhile, in the same (February 2022) draft ECD, the Committee described in section 4.41 the perceived merits of a vignette study (which are addressed further in §§9.20-9.25 below) in the following terms:

"*… Such a study would collect patient or expert experiences to form a detailed, qualitative description of each disease health state (a 'vignette'). The quality of life associated with each vignette could then be quantified, using established methods, preferably by the general population or alternatively by clinical experts, to provide an objective estimate of utility. … The committee considered that, if such a study was submitted, it may be possible to refine the QALY estimates and then reconsider with a higher degree of certainty the QALY gains and value for money of afamelanotide*."

7.6 CLINUVEL noted that the Committee's comments as to the potential utility of a vignette study were in direct conflict with its clearly-expressed conclusion in section 4.21 as to the usefulness of qualitative evidence, and pointed this out to the Chief Executive Officer of NICE by letter of 16 March 2022 (which is attached to this appeal letter).

The Committee's change of approach in July 2022

7.7 On 6 July 2022, the fourth Committee Meeting took place. At that meeting, in response to a question from CLINUVEL seeking clarification on the use of qualitative data, the Chair noted in the fourth Committee Meeting that there were two types of qualitative data: "structured" qualitative data, which could be accommodated by the Committee, and "unstructured" qualitative data, which could not. No further clarification was provided either during or after the meeting as to the boundary between these two purported types of qualitative data.

7.8 CLINUVEL accordingly wrote to the Chief Executive Officer of NICE, by letter dated 14 July 2022, again noting the tension in the February 2022 draft ECD, the comments during the fourth Committee Meeting and seeking an explanation as to the kinds of qualitative data that could be accommodated. The material part of CLINUVEL's letter is set out in point 14 of **Committee Papers 4**. It included this:

"*... [W]e have received no clarification from NICE as to:*

- *the definition of "structured" and "unstructured" qualitative data;*
- *where "structured" or "unstructured" qualitative data may be appropriately deployed;*
- *why the ECD dismissed all qualitative data in a broad – yet definitive – statement, and whether other such statements made by the Committee or NICE require similar clarifications;*
- *the reasons for the Committee's approach to qualitative data in general, and vignette studies in particular; or*
- *how NICE categorises the data provided by CLINUVEL to date.*

We note, in particular, that no clarification or definition of "structured" or "unstructured" qualitative data was present in the ECD, nor does one exist in any NICE guidance."

7.9 To date, there has not been a full and substantive reply to that letter. Instead, in September 2022, a further draft ECD was shared in which what had been section 4.21 of the February 2022 draft was replaced with the following (in what was now numbered section 4.25):

"*[The Committee] noted that relevant qualitative descriptions of health states associated with EPP could be used to elicit quantitative values (such as in a vignette study), which could be used in an economic model. It also noted that it was important to consider how the benefits of afamelanotide could be quantified as part of its decision making. The committee was also aware that the decision support unit had issued updated guidance on the use of qualitative evidence to inform generation of utility values in health technology assessment. It concluded that qualitative descriptions in the form of a vignette study could be used to inform the economic model.*"[10]

7.10 In point 8 of its response to the September 2022 draft ECD (see **Committee Papers 4**), CLINUVEL noted that the Committee's stated views were different to those that had been in the previous draft ECDs. NICE's response was, "*This previous statement concerning qualitative evidence has been updated with a statement that more clearly reflects committee's views*," and the text of sections 4.24-25 of the September 2022 draft ECD is now reproduced largely *verbatim* in sections 4.23-24 of the FED.

[10] The NICE Decision Support Unit guidance to which the Committee referred was dated 31 July 2020: see hiips://www.sheffield.ac.uk/nice-dsu/methods-development/measuring-health-related-quality-life.

The resulting lack of transparency

7.11 It can be seen from the foregoing that:

7.11.1 The Committee's stated position on the usefulness and uses of qualitative data has changed from one that, in effect, held that qualitative data could play no meaningful role in the central value for money analysis to one that recognised a potential role.

7.11.2 That having been said, the Committee clearly has in mind a typology/hierarchy of qualitative data: "unstructured" qualitative data are still of peripheral relevance; "structured" data are more useful; and certain types of "structured" qualified data – or to be precise, one particular such type, vignette studies – are so useful that they can be used for quantitative analysis.

7.11.3 Neither the (late) change in NICE's approach and methodology, nor the full typology/hierarchy nor the reasoning behind it has been explained in any detail, or published, by NICE.

7.12 As set out above, it is fundamental to fair consultation that consultees are made aware of the criteria that will be applied by the decision-maker, and in a timely fashion such that they can give a properly informed response. The Committee's changes of stated position and lack of coherent explanation have not been consistent with this obligation. To give two examples:

7.12.1 It is now clear that, in its initial (March 2022) response to the proposal for a vignette study, CLINUVEL was proceeding on an understanding of NICE's position that was not accurate. CLINUVEL pointed out that the enthusiasm to explore a vignette study to inform QALY values was misconceived because it was not consistent with the Committee's own approach and methodology. Had CLINUVEL understood that in fact the Committee does <u>not</u> have such a blanket approach to qualitative evidence, it could instead have directed its submissions so as to focus on NICE's actual views. In particular, CLINUVEL would have been better placed to explain why its EPP-QoL provided a more than sufficient alternative form of evidence. In short, CLINUVEL was placed at a disadvantage by NICE's unexplained methodological inconsistency and was undermined – as a result – in its ability to advance its case.

7.12.2 There are numerous respects in which the Committee's reasons for preferring certain forms of evidence over others are, in CLINUVEL's view, unreasonable.[11] More important, it has been very difficult for CLINUVEL to make effective representations without a full understanding of the typology/hierarchy of qualitative data that the Committee has applied. In particular, CLINUVEL remains unclear about (i) the relationship between "structured" and "unstructured" qualitative evidence (NICE has offered no explanation as to the apparently critical boundary between these two forms of data); and (ii) how each of these types of evidence falls to be considered relative to the various types of quantitative evidence before the Committee.

7.13 Unsurprisingly, the contradictions in the Committee's views; changes of position; and lack of clear explanations have contributed to a loss of confidence by CLINUVEL in NICE's process and decision-making, as expressed at the fourth Committee Meeting and in the correspondence to NICE's Chief Executive Officer on 14 July 2022.

The requirement of 'conscientious consideration' was not met [ground 1(a).2]

7.14 *T*he Committee's engagement with both the process and the evidence was not consistent with the fourth of the *Gunning* requirements set out above. As was set out in *R v London Borough of Barnet, ex p B* [1994] ELR 257 at 375C (commenting on the fourth requirement), "*the important thing is that the [authority]*

[11] For example, why exactly is a vignette study preferred to the data collection proposal that CLINUVEL put forward (FED, section 4.55) when the latter involves use of a partially validated tool (the EPP-QoL) and the former is a methodology unvalidated for use in EPP?

should have embarked upon the consultation process prepared to change course, if persuaded by it to do so."

7.15 Put simply, the Committee has not demonstrated that it would ever have been prepared to change course, in the light of the evidence presented to it. In particular, it has not been prepared to accept evidence provided to it that – on any view – meets some of the shortcomings in the existing evidence base in relation to EPP.

8. NICE ACTED UNFAIRLY BY REASON OF DELAY [Ground 1(a).3]

8.1 NICE is responsible for the timelines of its appraisals of technologies. The HST Process Guide provides in §25 that the core process lasts 17 weeks, with a timeline of 27 weeks in the event of public consultation, and a 7- to 15-week timeline for the "*Additional process*" post appeal.

8.2 In this case, a period of 230 weeks and 6 days (more than 4 years) has elapsed between the publication of the 2018 Decision on NICE's website (9 October 2018, which could be considered the commencement of the Additional Process) and the publication of the FED. This includes a period of 55 weeks between the third Committee Meeting (14 March 2019) and a formal notification to CLINUVEL that the COVID-19 pandemic was impacting upon NICE's review timelines (26 March 2020).

8.3 No reason has been provided for the delay beyond COVID-19, and even this reason is clearly not a partial, let alone a complete explanation. For example:

8.3.1 CLINUVEL received no appraisal-specific correspondence between 13 March 2020 and 11 May 2021, and no substantive correspondence until 20 December 2021, despite all other HST processes progressing during the same period. This was notwithstanding CLINUVEL seeking information and engagement in this time[12] and Mr Meindert Boysen (Centre for Health Technology Evaluation Director of NICE) reassuring it by email on 16 September 2021 that NICE would "*prioritise*" a reply to CLINUVEL's requests. NICE's formal response to the 14 September 2021 letter was received on 20 December 2021. In subsequent correspondence to CLINUVEL of 18 May 2022, NICE notes, "*following the delays caused by the COVID-19 pandemic, NICE recommenced the evaluation of afamelanotide at the end of 2021*".

8.3.2 NICE has subsequently suggested that in fact, the period of inactivity between March 2020 and May 2021 was a "*pause*", the purpose of which was to allow stakeholders to obtain and provide further evidence[13]. However, this was never communicated to CLINUVEL in March 2020, and indeed was first suggested after the "*pause*" had come to an end. CLINUVEL submits that this rationalisation of the "*pause*" was an *ex post* justification provided after the event to explain the considerable delay in making any progress.

8.3.3 In February 2022, by which time the NICE process was supposed to have resumed, NICE hosted a workshop, outside of the process, during which the newly assigned project manager requested a "*reset*" of the process and review. NICE has never provided an adequate explanation for what the "*reset*" would involve or why it was necessary.

8.4 In short, the Committee's conduct of the process was bedevilled by unjustified delays and has been greatly extended by a series of procedural steps that were either not explained and/or were clear deviations from the steps set out in the HST Process Guide. The Committee's retrospective attempts to justify or explain those delays is not satisfactory.

8.5 This delay has had multiple adverse consequences. Not only has this delay, along with deviations from the published process, deprived CLINUVEL of a fair opportunity to hear and address NICE's concerns as

[12] CLINUVEL provided detailed information to an interim project coordinator in May 2021, followed by correspondence to the Chief Executive Officer and Mr Boysen on 14 September 2021.

[13] Slides presented at the 8 February 2022 Workshop and in subsequent Committee Meetings.

required by the process but as a result, there are less than two years remaining of the ten years' orphan market exclusivity granted to SCENESSE® in 2014. CLINUVEL asks the Appeal Panel to note the European Commission's Rare disease website, which states:

"Patients suffering from rare diseases deserve the same quality of treatment as other patients within the European Union.

Given the small numbers of patients affected by rare diseases, the pharmaceutical industry has been reluctant in the past to invest in the research and development of medicinal products to treat them.

The EU introduced new legislation in 2000 with the aim of providing incentives for the development of medicines for rare diseases (so-called orphan medicinal products)."

8.6 CLINUVEL has been prevented from enjoying the benefit of the incentive conferred under the orphan legislation due to an unfairly delayed commissioning process. Thus the delay described above has frustrated an important public policy objective.

8.7 Finally, it is also fair to note that the delays in this case have been so significant that the methodologies applied by NICE for assessing products have changed: CLINUVEL has been required to meet a 'moving target' as a direct consequence of the Committee's unjustified delays.

9. THE FED IS IRRATIONAL IN MULTIPLE RESPECTS [Ground 2]

9.1 CLINUVEL submits that the FED is infected by multiple substantive errors. While these are enumerated individually below, and each is a ground of appeal in its own right, CLINUVEL also respectfully encourages the Appeal Panel to consider them in the round. Collectively, they reveal not only rigidity of thinking and misunderstandings about EPP but also patently, in the words of Sedley J (in *R v Parliamentary Commissioner for Administration ex p. Balchin*[14]), "*a decision which does not add up*".

The Committee's decision-making did not follow the relevant NICE Principles [ground 2.1]

9.2 In section 4.42 of the FED, the Committee noted and proceeded to consider CLINUVEL's position that it does not consider that the QALY estimates, and hence the ICERs, are appropriate to use for decision-making in this case.

9.3 The Committee began by recognising that the NICE Principles and Constitution require it to:

9.3.1 have regard to the broad balance between the benefits and costs of providing health services of social care in England; and

9.3.2 take account of our commitment under the NHS Constitution to provide 'the best value for taxpayers' money and the most effective, fair and sustainable use of finite resources'.

9.4 The Committee emphasised the statement in NICE's Principles that "*[i]f possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio (ICER). This is based on an assessment of the intervention's costs and how much benefit it produces compared with the next best alternative*." (§23; Emphasis added) In this case, SCENESSE® being the only medicine authorised to treat EPP, an incremental comparison to the next best alternative is not possible – or at least, not in any usual or meaningful sense. The "*next best alternative*" is no treatment at all. This fact is not expressly acknowledged in this section of the FED.[15]

9.5 Nor in section 4.42 is there reference to, or acknowledgment of, §25 of NICE's Principles, which states, "*NICE's recommendations should not be based on evidence of costs and benefit alone. We must take into*

[14] [1998] 1 PLR 1, [27].

[15] Or, indeed in the critical sections evaluating cost-effectiveness and setting out the reasons for the decision and the Committee's conclusion.

account other factors when developing our guidance." Instead, the Committee, having "*recalled the crucial importance of considering value for money in a fair and consistent way as part of this remit*" and set out §23 of NICE's Principles, continues with the recognition that value for money must remain an important (but not the only) part of the decision in this case and emphasises (by reference to section 4.58) that the ICER was not the only contributor to its view on value for money.

9.6 CLINUVEL submits that the Committee's approach in fact deviated from the NICE Principles set out above in at least three respects.

9.7 *First*, NICE did not in fact have regard (alternatively, adequate regard) to a broad range of factors or seek to balance the benefits and costs of providing afamelanotide in England. As is clear from the points already discussed under **ground 1(b)** above, the considerations that actually influenced the final decision not to recommend afamelanotide focused narrowly on ICERs to the exclusion of other relevant factors.

9.8 *Second*, similarly, NICE does not appear to have given any (alternatively, any adequate) consideration to best value for taxpayers or the effective, fair and sustainable use of finite resources or indeed to any other factors. It is accepted by NICE that SCENESSE® is the only commercially available treatment for EPP. As such, treatment with SCENESSE® for EPP patients is potentially life-changing and enables them to engage in society more readily without suffering from phototoxic reactions. Again, this weighty factor was in substance overlooked by reason of the Committee's ICER-driven analysis, which did not seek to consider the merits or benefits of the product balanced against costs.

9.9 *Third*, although (per section 4.42 of the FED) NICE's Principles state that "*[t]he primary consideration underpinning our guidance and standards is the overall population need,*" there is again no evidence of this having featured as a consideration in the decision-making process.

It was unreasonable for the Committee to conclude that afamelanotide could not be recommended for funding on the basis of the ICERs falling outside the normal range in the HST Process Guide [ground 2.2]

9.10 §46 of the HST Process Guide provides that, as part of its consideration of value for money, the Committee "*must give consideration to the balance of the costs associated with the technology relative to the benefits it provides*". §46 further states that, in order to do so, the Committee will consider the ICER, expressed as an incremental cost per QALY gained.

9.11 §50 indicates specifies that a "*most plausible ICER*" of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources.

9.12 That having been said, there is nothing in the HST Process Guide to suggest that technologies for which the ICER falls outside the normal or expected range cannot, in principle, be recommended by NICE; in other words, there is nothing that mandates a cut-off at above £100,000 – even outside the QALY weighting process described in §§51-54. Instead, in §55 of the HST Process Guide, it is made plain that there is a judgment for the Committee to make, the factors relevant to which include

"[w]hether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained"; and

"*[t]he 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*".

9.13 That is as it should be – the merits and benefits of each product should be considered by NICE in the exercise of its discretion when making funding decisions. It is CLINUVEL's understanding that in previous years HSTs have been recommended in circumstances where it is not possible to identify a

plausible ICER within the normal range (see, for example, NICE's recommendation in respect of Strimvelis for treating adenosine deaminase deficiency-severe combined immunodeficiency).

9.14 CLINUVEL has already explained in §§6.3 above that NICE's duties under the Equality Act required it to make reasonable adjustments – or to 'flex' - so as to at least consider recommending for funding a technology with ICERs of over £100,000. But in any event, CLINUVEL submits that in all of the circumstances of this case, quite apart from the requirements of the Equality Act it was in any event unreasonable for the Committee to have adhered rigidly to the £100,000 threshold:

9.14.1 The Committee accepted that the ICERs it relied upon in reaching its decision as a part of a reasonable adjustment given the nature of the condition ranged from £133,748 to £253,676 per QALY gained. The Committee considered that £133,748 per QALY gained was "*a potentially plausible ICER*" and, for the reasons set out in §§6.17 above, the Appeal Panel should proceed on the basis that £133,748 is no less plausible than any other of the various ICER estimates in the FED. (We note that CLINUVEL had previously presented DALY scenarios which arrived at costs below a £100,000/DALY threshold and that the uniform pricing presented by the Company, if used in the plausible ICER scenario, resulted in an ICER of £121,233 per QALY gained.)

9.14.2 While at the lower end, the QALY accepted by NICE is just outside the normal range (by some £33,748, or £21,233). Clearly, therefore, it was necessary for the Committee to consider the factors in §55 of the HST Process Guide.

9.14.3 There was no such consideration. There is no mention, other than in section 4.42 of the FED, of patient need (which, under NICE's Principles, should be the primary consideration in the decision-making process: see above); of the nature of the EPP patient population; of the fact that clinical trials likely underestimate the benefits of the product; or of the fact that there is no alternative therapy available for EPP patients. This was in the face of evidence which showed that treatment with afamelanotide provides photoprotection and enables EPP patients to participate more fully in society, including by way of increased employment, study, and family opportunities.

9.15 In the circumstances, the Committee's decision not to recommend afamelanotide for funding on the basis of the ICERs was inadequately explained; did not address adequately or at all the considerations set out in the HST Process Guide or the NICE Principles; and was unreasonable.

The reasons in the FED for refusing to recommend an MAA were illogical [ground 2.3]

9.16 A particularly acute example of the lack of logic in the Committee's recommendation was the proposed CLINUVEL MAA. The reasons for considering an MAA include (per §57 of the HST Process Guide):

"*- the need for and potential value to the NHS of additional evidence that can inform the future development of NICE guidance and clinical practice on the use of the technology;*

- the uncertainty in the analysis and what is needed to reconsider the decision in the light of research findings;

- whether the data collection is feasible;

- the extent of irrecoverable costs incurred from introducing the technology and plans to mitigate this risk"

9.17 In this case, the need for additional evidence and uncertainty was abundantly clear; the Committee accepted that CLINUVEL's proposed data collection arrangement "*could … generate utility values*"; and the budget impact for the NHS was [redacted]. But the Committee

nevertheless concluded that managed access could not be recommended in view of the ICERs exceeding £100,000.

9.18 Quite apart from underlining that the Committee simply cannot have considered other factors beyond the ICERs (contrary to its duties under the NICE Principles and the HST Process Guide), this reasoning is plainly circular: the fact of high (but unreliable) estimated ICERs precluded an option that was itself intended to explore the availability of better data to improve the estimates.

9.19 Indeed, far from seeing an MAA as a potential way to address the need for additional evidence, the Committee instead chose to highlight as a "*new opportunity*" the IMF (see section 4.54), suggesting that this was the appropriate route for managed access. CLINUVEL's proposals were therefore considered under the criteria applicable to the IMF, which places a well-defined upper threshold of £100,000 per QALY gained on the products that will be considered for managed access. It was therefore unsurprising (and would have been foreseeable to the Committee) that, notwithstanding CLINUVEL's attempt to put forward innovative, risk-sharing proposals to bring an MAA within the IMF's commercial parameters, it did not prove possible to reach agreement with NHS England.

The emphasis placed by the Committee and NICE on the importance and usefulness of a vignette study to inform the QALY was irrational [ground 2.4]

9.20 Throughout the process of appraisal for afamelanotide, the Committee – notwithstanding its insistence that quantitative evidence, relying on established, validated tools which aligned to NICE's preferred modelling approach were preferred[16] – focused on the use of vignette studies as a possible method by which the effectiveness of afamelanotide could be evaluated. On several occasions during the review, NICE staff made it clear to the Company that the completion of vignette study was necessary to obtain a MAA. During the Stakeholder Workshop meeting of 8 February 2022, slides presented by NICE stated that "*a vignette study to help quantify the benefits of afamelanotide in terms of QALYs would be required before any MAA could be agreed in order to improve the value for money estimates*". CLINUVEL raised this issue with NICE's Chief Executive Officer in correspondence on 16 March 2022, which went unaddressed in the response received from NICE on 18 May 2022.

9.21 In section 4.49 of the FED, the Committee professed itself to be "*disappointed that the company had chosen not to do a vignette study*" and indeed, in section 4.54, it commented about CLINUVEL having been "*not willing to establish a vignette study … to help quantify the benefits of afamelanotide in terms of QALYs*". The impression conveyed to the reader is that the Committee clearly explained to CLINUVEL that a vignette study would be beneficial and expected CLINUVEL to prepare a vignette study comprising a questionnaire of patients, and that CLINUVEL's decision not to do so counted against it in the Committee's decision-making. That approach was unreasonable.

9.22 The Committee had before it numerous patient testimonies which, it is submitted, adequately demonstrated the impact of EPP and the value of treatment with afamelanotide. CLINUVEL had already obtained stakeholder input on the way in which its evidence was generated, rendering the utility of a further, as yet unstructured, qualitative vignette study questionable. More importantly, as reflected in section 4.49 of the FED, the use of vignettes was the subject of concerns expressed by stakeholders (including patient experts); as a small-scale, qualitative approach unvalidated for use in EPP, risked being not only inappropriate but also unreliable in this disease area; and would conflict with NICE's standard approach. This includes the stated view of the ERG that data collection should use EQ-5D (see slide 21 Committee slides)[17].

9.23 In the face of this formidable array of difficulties, the Committee's continued demand for a vignette study even in preference to other forms of quantitative data is, with respect, difficult to fathom.

[16] Indeed, its insistence at least until July 2022 that qualitative evidence could not inform economic modelling: see §§7.9 above.
[17] Vignettes would also be costly to perform and CLINUVEL notes that in HST8, company vignettes were dismissed by ERG and not seen to generate robust data.

Compare, for example, the FED's summary of the EPP-QoL at section 4.18, in which the Committee is severely critical of a quantitative model which has been partially validated for the condition, with the uncritical explanation of the merits of vignettes in the latter part of section 4.49. The contrasting approaches taken by the Committee to the EPP-QoL and vignette studies lacks any cogent basis.

9.24 To take another example, the Committee rejected data from the largest individual cohort study on EPP patient outcomes (Wensink et al. 2020) reflecting data from the post-authorisation safety study ("**PASS**") and European EPP Disease Registry CLINUVEL was required to undertake, whilst at the same time seeking to push CLINUVEL to conduct a study that would be smaller in scale and scope.

9.25 CLINUVEL maintains that no reasonable Committee could have chosen to dismiss the relevance of the various models and data sets that were put forward by stakeholders to seek to explore the proper disease burden on EPP patients whilst claiming to be "*disappointed*" at CLINUVEL's decision not to perform new, untested, small-scale studies which did not fit NICE's preferred evidence base that would have likely produced less robust data.

The failure to place any (or any adequate) weight on treatment adherence data was irrational [ground 2.5]

9.26 As part of the evidence base for the use of afamelanotide, CLINUVEL presented data that showed 98.5% of patients continued to adhere to the treatment year-on-year. These data serve as a powerful indicator of the effectiveness of the treatment. CLINUVEL argued that patients would not continue on treatment at such a high level if it were ineffective.

9.27 In the FED, the Committee noted in section 4.27 that treatment adherence is "*not a direct marker of effectiveness*". That is true as far as it goes. However, there is no further reference made to the adherence data in the remainder of the FED. It is therefore apparent that treatment adherence not being a direct marker of effectiveness was considered by the Committee to be sufficient reason not to consider it at all in any of its analysis of effectiveness or decision making.

9.28 This is a *non sequitur*. There is clear evidence in the literature that adherence to treatment in patients with chronic conditions is impacted by the actual or perceived effectiveness of the intervention[18]. Put another way, while adherence data may not be a direct marker of effectiveness, a lack of treatment adherence has been shown to correlate to an effect or lack thereof, either directly or in patients' perceptions of efficacy. It therefore does not follow that the indirect nature of the relationship renders treatment adherence data unreliable and/or uninformative. The FED fell into a clear error when it dismissed the evidence altogether for this reason.

9.29 Particularly given all the other data accepted by the Committee, the Committee's insistence that even indirect, qualitative tools such as a vignette study held value, and the findings of the EMA, it was irrational for the Committee not to consider treatment adherence data as a useful indirect measure of effectiveness as part of its review.

The failure to place any (or any adequate) weight on data from post-authorisation and observational studies was irrational [ground 2.6]

9.30 Five peer-reviewed publications were submitted by a patient stakeholder group during the review process: Wensink *et al* (2020), Wensink *et al* (2021), Wensink *et al* (2022), Barman-Aksoezen *et al* (2020) and Minder *et al* (2021). The FED (section 4.30) notes that "*none of the data [from these publications] could be used to inform the economic model*". In essence, the Committee, having recited in

[18] See, for example, factors affected intentional non-adherence discussed in:
George et al (2007). Adherence to disease management programs in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 23(3):253-262.
Emamika et al (2022). How Can We Enhance Adherence to Medications in Patients with Systemic Lupus Erythematosus? Results from a Qualitative Study. *J Clin Med.* 11(7):1857.
Saglam-Aydinatay & Taner (2017). Oral appliance therapy in obstructive sleep apnea: Long-term adherence and patients' experiences. *Med Oral Patol Oral Cir Bucal.* 23(1): e72–e77.

section 4.29 a series of arguments in relation to these peer-reviewed papers, accepted uncritically all of the ERG's points. It was irrational for the Committee to do so, as the ERG's reasons were plainly deficient, as discussed in the Company's response to the September 2022 ECD and during Committee Meeting 5:

9.30.1 Wensink *et al* (2020) is the largest single EPP cohort study ever reported. This peer-review study presents comparative data (individual patients compared to baseline) incorporating EPP-QoL data and additional exposure data which suggested that EPP patients largely normalised their sunlight exposure time during treatment. The FED states that there is an "*absence of any alternative critical interpretation of Wensink et al. (2020) provided by the company*", which is why the ERG took its view – a position unchallenged by the Committee or the FED. This is not accurate. The study presented in Wensink *et al* (2020) is the PASS, extensive details of which have been provided by CLINUVEL and discussed at length, including the validity of EPP-QoL and exposure data, the rationale for not including a "*control group*" (in line with the EMA decision), the available patient population, and the recall period of tools used.

9.30.2 Indeed, the fact that the Committee in the FED section 4.41, relied on Wensink *et al* (2020) as a justification for its decision to use 4 implants per annum to inform its decision-making suggests that the Committee viewed the data from the study as being generalisable to clinical practice in England.

9.30.3 Barman-Aksoezen *et al* (2020) and Wensink *et al* (2022) present additional observational data, seeking to quantify EPP patient light exposure following afamelanotide treatment. It is relevant to note that the inability of EPP patients to expose to light is a key component to their disability, and data seeking to quantify this could be used to inform economic models focused on the impact of the disease beyond quality of life (such as by facilitating freedom from anxiety or pain, freedom of movement, access to work or study opportunities or ability to participate in society). The critiques of the ERG – accepted uncritically in the FED – unreasonably fail to recognise the potential of the data in these studies to inform economic models, including in circumstances where the FED itself (section 4.7) laments the lack of exposure data to inform characteristics of the disease.

9.30.4 Minder *et al* (2021) provides evidence of a hepatoprotective effect of afamelanotide in EPP patients. The nature of liver failure in EPP – although a rare complication – may have a considerable impact upon the economic burden of the disease, due to the potential need for a life-saving liver transplant and subsequent lifelong immunosuppression. This is therefore a further point that could have been used to inform an economic model, particularly in view of the relative simplicity of the protoporphyrin IX ("**PPIX**") test used in Minder *et al* (2021).

9.30.5 The ERG is dismissive of the value of this study, noting that "*tests other than those used in the study are likely to be used to assess liver damage*". CLINUVEL addressed this issue in its response to the ECD, with the point subsequently dismissed by the Committee in its response published on 13 March 2023. CLINUVEL reiterated evidence in Minder *et al* (2021) that PPIX and aspartate aminotransferase ("**AST**") are valid measures of liver dysfunction for EPP patients.

9.30.6 NICE has not issued guidance on liver function tests, either for EPP specifically or in the general population. The *British Journal of Medicine* released best practice guidelines for the evaluation of liver dysfunction in January 2023 which recognise that AST is amongst the key markers of liver disease and dysfunction. Unsurprisingly, PPIX was not listed as this is not seen as an elevated marker of dysfunction in the general population but, as explained in Minder *et al*: "*[t]he risk of liver disease increases with increasing erythrocytic PPIX concentrations which varies from patient to patient*". This comment references Anstey and Hift (2007), a key reference article on EPP and liver disease, written by UK experts which delves into the complexities of liver dysfunction in EPP and recognises the role of PPIX.

9.30.7 CLINUVEL acknowledges that other measures may be relevant to assessing liver damage in the general population. The difficulty is, though, that the ERG, while dismissing the value of PPIX and AST, provided the Committee with no evidence specific to EPP patients. There was therefore a potentially relevant economic benefit; a potentially useful tool; and no proffered alternative – even imperfect – to address the issue.

9.30.8 Faced with this situation, the Committee's reaction was not to do the best it could to take Minder *et al* (2021) into account or to reflect the issue of liver failure in its analysis but instead to recognise the potential protective effect of afamelanotide; state that "*the extent was unknown*"; and make no further reference to it.

9.31 Stepping back, despite the FED stating that Committee would "*take the study results into account*" (section 4.30), it is clear that because the Committee considered (wrongly) that the data from these studies could not inform the economic model – the only decision-making tool actually used by the Committee to reach its decision – in reality, none of the evidence actually featured in the decision-making. In the light of the points made above, the Committee's approach and conclusions were irrational and inadequately reasoned: the FED is "*a decision which does not add up*".

The decision to disregard the EPP-QoL tool reflected a factual error [ground 2.7]

9.32 The FED states in section 4.18 that "*[t]he condition-specific QoL questionnaire, EPP-QoL, was developed by the company*". In fact, throughout the appraisal process, CLINUVEL has made it clear that the EPP-QoL tool was developed alongside and in conjunction with independent EPP experts. Indeed, the evidence submitted by stakeholders to the Committee included peer-reviewed articles demonstrating the role played by EPP experts in the development of this tool. The Committee's assessment of this evidence rested, therefore, on a clear factual error.

10. CONCLUSION

10.1 For all the reasons set out above, CLINUVEL appeals the FED decision. We respectfully request a re-evaluation of the product on the basis of the approach as outlined in this submission. CLINUVEL reserves its rights.

Yours faithfully

[redacted]
Director of Global Operations,
CLINUVEL Group

Dr Samantha Roberts
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Level 1A, City Tower
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United Kingdom

Sent by email to [redacted]

CC: [redacted]

16 March 2022

Re: NICE evaluation: Afamelanotide for treating erythropoietic protoporphyria [ID927]

Dear Dr Roberts,

Background
CLINUVEL is the marketing authorisation holder for the novel product SCENESSE® (afamelanotide 16mg) which is approved for the prevention of phototoxicity in adult patients with the rare disorder erythropoietic protoporphyria (EPP). SCENESSE® is the only approved medication for the estimated 500 EPP patients residing in England. It is believed that less than 400 adults would be eligible for treatment.

SCENESSE® was approved in Europe in 2014 and has been subject to NICE review since 2015. In its initial review of the topic, the Southampton Evidence Review Group recognised the benefit of the product to EPP patients and aligned its interpretation of evidence to the review and findings of the European Medicines Agency (EMA). The estimated annual budget impact across the first three years of introducing the product for English patients would be [redacted], as confirmed by NICE's own appraisal of the Budget Impact Template.

Various errors have been made by NICE in the review which, by NICE's own admission, have not been rectified. Further, NICE has consistently and deliberately sought to delay or frustrate its review of afamelanotide, to the detriment of EPP patients and causing material damage to CLINUVEL. NICE has also ignored its own Appeal Panel, which found on 31 July 2018 that the Highly Specialised Technologies (HST) Committee breached the UK Equality Act (2010), excluded patients, and unreasonably ignored evidence provided to it in arriving at its decision.

During the Appeal Panel, and within the context of the questions posed about how he had assessed a handicap in rare diseases or unmet diseases, Peter Jackson answered that the HST Committee *"lazily"* interpret disabilities as *"those which are visible"*. To the amusement and horror of patients and physicians present, Mr Jackson had disclosed his decision-making process.

Attempts to engage NICE have often been met with dismissal or refusal to acknowledge correspondence. At various points in time, Meindert Boysen stated that price negotiation would be fruitless since the price commanded by the Company was too high for NICE to consider. When CLINUVEL sought to negotiate directly with NHS England, Mr Boysen and Sheela Upadhyaya did not wish to cooperate, as they deemed this would not lead to positive outcome. After months of insistence from the Company, exactly one phone call was eventually held with NHS England where Mrs Upadhyaya had clearly prebriefed the manager, and the phone call lasted a matter of minutes. These examples are not exhaustive.

NICE, led by Peter Jackson and Meindert Boysen, have skilfully delayed the review of SCENESSE® such that CLINUVEL would not be in the position to seek judicial review and civil action against the errors made in this case.

Market access in Europe
CLINUVEL has publicly stated and maintained since 2014 that it would treat all insurance groups and state insurers equitably and transparently by charging one uniform drug price without providing rebates, discounts or paybacks. This has been embraced by 16 countries as a breakthrough in drug pricing, whereby CLINUVEL has disclosed its invoices, payments and financial statements. Uniquely, and setting the Company apart from any of its peers, the Company has maintained a uniform price within the European Economic Area and Middle East for the product since 2017, without annual CPI increases.

The Company's transparent approach to pricing has been repeatedly rejected by Messrs Jackson and Boysen, asking us to *"lower the price by an order of magnitude"*.

Stakeholder workshop
On 8 February this year, four years after the Appeal Panel upheld three grounds of appeal, the Company attended a "stakeholder workshop" meeting for the topic, a discussion which should have been held in March 2020. The organisation of this workshop – led by Richard Diaz and Ms Upadhyaya – was shambolic and once again emphasised NICE's disdain and lack of respect for EPP patients. Mr Diaz noted several times, for example, that his intention was to "reboot the topic" and that "no preparation was necessary" on the part of attendees.

Throughout the discussion it was made clear by Mr Diaz and Ms Upadhyaya that the HST Committee feels it has addressed the findings of NICE's Appeal Panel in 2018 and will only engage with CLINUVEL on the review of afamelanotide on two conditions:

I. CLINUVEL reduces the price of SCENESSE® offered in England; and
II. CLINUVEL completes a qualitative "vignette" study.

The demand to complete a further study not only contradicts the findings of the EMA but conflicts with section 4.21 NICE's draft February 2022 ECD which states *"qualitative evidence, even when formally analysed, could not be directly used in quantitative analyses or to quantify the size of the treatment benefits [for EPP patients]. The committee also noted that such evidence could not be directly used in an economic analysis".* NICE's further request for a vignette study is farcical since Messrs Jackson and Boysen have already expressed not wanting to reimburse the product.

False and fictitious claims on SMC agreement
CLINUVEL has received no further correspondence from Mr Diaz or Ms Upadhyaya. The Company has been advised, however, that Mr Diaz has spoken with representatives of EPP patient associations. During these discussions, Mr Diaz is reported to have made comments speculating on CLINUVEL's reimbursement agreement with the Scottish Medicines Consortium (SMC). We note that SMC agreements are confidential according to legally binding contracts.

Any claim that CLINUVEL has offered or accepted a discount on the price of SCENESSE® in Scotland is false.

Final Evaluation Determination (FED)
An objective reader, skilled in the field and looking at this dossier, detects the tactics deployed by Messrs Jackson and Boysen without adhering to their own Appeal Panel. The result is that EPP patients have been deprived of treatment since 2014.

After seven years of review there is no constructive dialogue that will come from further interaction between CLINUVEL and NICE.

The Company kindly asks you to intervene and issue the FED immediately, such that we can initiate litigation.

We reserve all rights.

Yours sincerely,

[redacted]

Director of Global Operations,
CLINUVEL Group

Dr Samantha Roberts
CEO
National Institute of Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester, M1 4BT
United Kingdom
Sent by email to [redacted]

CC: [redacted]

14 July 2022

Re: NICE evaluation: Afamelanotide for treating erythropoietic protoporphyria [ID927]

Dear Dr Roberts,

Background
Following the fourth Highly Specialised Technology (HST) Committee Meeting on 6 July for the appraisal of afamelanotide, CLINUVEL is compelled to again request your intervention in order to arrive at a fair, transparent, and reasonable decision on treatment access for the 400 erythropoietic protoporphyria (EPP) patients in England. CLINUVEL would wish to work with NICE in order to achieve such a decision, in the interests of patients. We are, however, frustrated by the approach of both the Committee and NICE secretariat, who have so far insisted on an inflexible and, we believe, discriminatory adherence to a methodology which was not designed for evaluating conditions such as EPP. As a result, as explained at the 6 July meeting, we have lost confidence in NICE and the HST process.

Contradictory approach to evidence demanded by NICE
The European Medicines Agency, in granting approval to afamelanotide for EPP, found that the current state of scientific knowledge, tools and instruments, cannot measure the impact of EPP or its treatment. Despite this, NICE and the Committee have insisted that CLINUVEL conduct a vignette study – an approach which seeks to quantify qualitative data – to support its submission. No evidence has been provided by the Committee that vignettes are an appropriate tool for use in EPP or would actually address the Committee's concerns on the appraisal. It is our view that no such evidence exists. It has been made clear to the Company, however, that NICE will not consider the appraisal further without a vignette study being conducted.

In parallel with the Committee's position that a qualitative vignette study is the only option, the Committee also stated in the February 2022 draft ECD the conflicting position that *"qualitative evidence, even when formally analysed, could not be directly used in quantitative analyses or to quantify the size of the treatment benefits* [for EPP patients]*. The committee also noted that such evidence could not be directly used in an economic analysis"* (ECD 4.21).

You will appreciate that this position contributed to CLINUVEL's loss of confidence in NICE's process and decision makers, given that the approach of the Committee:

i. contradicts all the evidence available to the Company and the conclusions of the European Medicines Agency; and

ii. insists that CLINUVEL produces data from a qualitative vignette study even though such methodology is unvalidated in EPP, and while simultaneously rejecting the use of qualitative data analyses in economic analyses.

We raised the contradiction in NICE's approach in our correspondence to you of 16 March, however we received no response to this enquiry.

During the 6 July discussion our team's enquiry on this contradictory approach was patronisingly dismissed by the HST Committee Chair, Dr Jackson, despite his recognition that the ECD was unclear on this point and apology for his role in drafting the ECD. When asked to clarify, Dr Jackson stated that the Committee made a distinction between "structured" qualitative data, which could be accommodated by the Committee, and "unstructured" qualitative data, which could not. This was the first time that such a distinction had been communicated to CLINUVEL, despite enquiries in previous correspondence. Furthermore, we have received no clarification from NICE as to:

- the definition of "structured" and "unstructured" qualitative data;
- where "structured" or "unstructured" qualitative data may be appropriately deployed;
- why the ECD dismissed all qualitative data in a broad – yet definitive – statement, and whether other such statements made by the Committee or NICE require similar clarifications;
- the reasons for the Committee's approach to qualitative data in general, and vignette studies in particular; or
- how NICE categorises the data provided by CLINUVEL to date.

We note, in particular, that no clarification or definition of "structured" or "unstructured" qualitative data was present in the ECD, nor does one exist in any NICE guidance.

Despite the confusion in the position of NICE and the Committee, the response to the issue on 6 July from both Dr Jackson and NICE's representative Ms Knight was not to provide an explanation of either the matter itself, or the failure to respond to our letter of 16 March 2022. Rather, Dr Jackson and Ms Knight simply suggested that the Company's view was inconsequential, as we had not followed the formal submission response process for the ECD. This issue is addressed in further detail below.

We finally note that the strongest advocate on the Committee for the vignette studies is Professor Akehurst. We have previously expressed concerns in relation to Professor Akehurst's potential conflict of interest in the context of this evaluation and believe these remain valid, even though they have been rejected by NICE's executive in previous appeal processes.

Equality Act 2010

It is CLINUVEL's contention (a view shared by other consultees on 6 July) that the way in which NICE's procedures are being applied to this evaluation breaches the Equality Act 2010.

In the context of an earlier appeal, NICE's Appeal Panel upheld the Company's point that the Committee unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities. The Appeal Panel noted that, in response to a question on whether the Committee considered EPP a disability, "*Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the [Equality] Act*" as it was not a *"visible"* disability. The Appeal Panel's findings further state:

> "*The panel could not see evidence of consideration of NICE's duties under the Act with respect to the use of afamelanotide in EPP specifically, elsewhere in the documents provided. Furthermore, the evaluation committee confirmed during the hearing that they had not taken into account any anti-discrimination legislation in reaching their decision…. the panel therefore concluded that NICE had not demonstrated adequate consideration of the legal obligations placed on it as a public authority".*

Despite the decision of the Appeal Panel, we believe that the Committee has still not properly taken into account its legal obligations as a public body under the Act. The fact that NICE has not recognised its duties (or those of the Committee) in this respect is demonstrated by a letter dated 18 May 2022 from NICE to CLINUVEL

where NICE asserts, despite the clear wording of the decision quoted above, that the Appeal Panel "*did not state that the committee breached the Equality Act*". If this reflects the advice given by the Institute to the Committee, there seems little hope of a fair and lawful outcome to the current evaluation, nor one that properly reflects the situation of patients with EPP and makes appropriate adjustments for their disabilities.

The above concerns were confirmed by the discussions at the 6 July meeting, where Dr Jackson asked CLINUVEL to define the unique characteristics of EPP (a repeat of an exercise undertaken in Committee Meeting 3 in 2019). At no point in time did Dr Jackson, or other Committee members, seek to address the fundamental issues underlying this evaluation relevant to NICE's obligations under the Act, including, but not limited to: why inflexible application of the HST process cannot capture, quantify and reasonably assess the impact of EPP on patients; and what evidence-based, reasonable adjustments can and should be made to meet the specific needs of EPP patients.

Process failures

We have previously raised concerns about NICE's willingness to work with stakeholders. These concerns, including NICE's unwillingness to engage in correspondence, remain unaddressed. Our examples here are not exhaustive.

On several occasions during the 6 July meeting, Dr Jackson and Ms Knight sought to deny the Company the opportunity to address matters raised in discussion. Dr Jackson repeatedly insisted that Company representatives be "brief" and Ms Knight cut off the Company's legal representative on several occasions when seeking to exercise their right to address procedural shortfalls.

Further, both Dr Jackson and Ms Knight argued that the Company had failed to submit a formal response to the ECD, and suggested that it was only through this standard communication route that the Company could engage NICE. This contradicts NICE's previous statements – including at the February 2022 Workshop – that the Company could approach NICE directly and that such engagement would be welcomed and appropriate. We note that correspondence was sent to NICE on 16 March, prior to the ECD response deadline, which was referenced by the Committee as part of its formal presentation on 6 July, even though CLINUVEL received no response to issues raised in that letter.

Pathway forwards

CLINUVEL stated in the 6 July meeting that it has lost confidence in the process and decision makers responsible for the review of afamelanotide in England. Despite this loss of confidence and, as indicated at the beginning of this letter, CLINUVEL remains willing to co-operate with NICE to reach a fair outcome to the current evaluation – one consistent with the arrangement agreed in Scotland and treating NHS England equally and transparently with all other payors. We consider that this can be achieved through a flexible and pragmatic approach to the assessment of afamelanotide, making necessary adjustments to accommodate the unique situation of English EPP patients and their disability.

At this stage, however, it is our view that a fair and transparent outcome to this evaluation can only be achieved through your personal intervention. We therefore ask for a direct discussion with you to review possible pathways forwards. If you are willing to participate in such a discussion, we ask that you please propose some convenient dates and times. We look forward to receiving your response to this letter.

Yours sincerely,

[redacted]

Director of Global Operations,
CLINUVEL Group