Appeal letter: International Porphyria Patient Network (IPPN)

23 March 2023

Dr Mark Chakravarty

Lead Non-executive Director NICE Appeals – Technology Appraisals and Highly Specialised Technologies

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Dear Dr Chakravarty

Re: Final Evaluation Determination – Afamelanotide for treating erythropoietic protoporphyria [ID927]

The International Porphyria Patient Network (IPPN) is a not-for-profit organisation which provides cross-border support and counselling to patients suffering from porphyria and porphyria patient associations in scientific, medical, and healthcare policy matters. The members of the IPPN are patients with porphyria and people interested in the porphyrias and have professional backgrounds in areas such as medicine, natural and social sciences, economics, and statistics. The IPPN is a stakeholder in the appraisal of two highly specialised technologies, i.e., afamelanotide for treating erythropoietic protoporphyria (EPP; ID927) and givosiran for treating acute hepatic porphyria (HST16). For the appraisal of afamelanotide, the IPPN contributes the unique perspective of patients under long-term treatment (≥ two years) with afamelanotide, the first and currently only approved

treatment for EPP. Moreover, several European countries, for example Norway, follow NICE recommendations or align their assessment with the Guidelines published by NICE. Therefore, the IPPN also acts in the interest of international patients indirectly affected by the appraisal at NICE.

Since their early childhood, patients with EPP suffer from incapacitating phototoxic burn injuries in their blood vessels which start after a few minutes in sunlight and even certain artificial light sources, in particular the increasingly used energy saving light bulbs. The associated severe neuropathic pain is not responsive to pain treatments and requires several days to resolve. Under treatment with afamelanotide, the tolerance to sunlight is increased to around median 3 hours (as has been shown in observational studies testing new endpoints) – which is sufficient time to fully function in daily life. Long-term treatment allows the patients to overcome their ingrained light avoidance behaviour and anxiety to expose themselves to sunlight, thus experiencing the full benefit of the afamelanotide treatment effects and a near-normalisation of all aspects of their lives. Afamelanotide has been approved in 2014, however patient in England and Wales are still denied access to this highly effective and beneficial treatment. The negative recommendation for funding of afamelanotide by the NHS disadvantages these patients, as afamelanotide is available to patients with EPP in the USA and several European countries, including The Netherlands and, on a provisional basis, Scotland – both countries in which health benefits are assessed in Quality-Adjusted Life Years (QALYs).

As discussed at the last Appeal Hearing in July 2018, the increase in daily time in sunlight as measured in the pivotal trial puts the patients under treatment with afamelanotide in the normal range for this measure. (NICE 2018, Appeal Decision p. 12 ¶ 70). This was reflected in “The appeal panel's conclusion that it was unreasonable for the committee to state that the trial results show small benefits with afamelanotide” (BAD 2.2 and 2.3, IPPN 2.2). (NICE 2018, Appeal Decision p. 20¶ 122). Despite this conclusion of the appeal panel and additional published peer-reviewed evidence on long-term treatment benefits and newly developed endpoints to measure the sunlight

tolerance under real world conditions, in their current FED the HST committee still questions the benefit of the treatment which is assessed as “highly uncertain”. (NICE 2023, ID927 FED p.1)

Moreover, in the appeal decision, the panel had asked the HST committee to address: “The failure to demonstrate adequate consideration of the legal duties and obligations placed on it as a public authority under the Equality Act (CLINUVEL1b.1 and IPPN 1b.1). The appeal panel considers that this is likely to include express consideration of whether the methodology used in the evaluation discriminates against patients with EPP and if so what reasonable adjustments should be made.” (NICE 2018, Appeal Decision p. 20¶ 122). Drawing from this upheld appeal point, the IPPN systematically compared publicly available information of previous appraisal procedures of highly specialised technologies with the evaluation of afamelanotide. Several of the currently submitted appeal points are based on the analysis of the consistency in assessing the evidence between the appraisals. Our comparative analysis is under no circumstances meant to question the validity of the positive recommendation for funding of the other appraisals of highly specialised technologies.

The IPPN would like to state that they have no interest in afamelanotide other than supporting all patients with EPP to access this treatment which we know is life changing from own experience. In fact, two members of the IPPN are researchers in the field of the porphyrias and have published peer-reviewed articles on new pathophysiological mechanisms in EPP and alternative treatment options, one of which (bitopertin) is currently tested in phase II clinical trials. Further, the IPPN does not aim to achieve “access at all costs” and does understand the challenges when distributing limited healthcare resources. In fact, our patient organisation even conducted an EQ-5D feasibility study with patients under long-term treatment with EPP to provide the committee with more suitable evidence for their decision making. However, we are under the strong impression that in the current appraisal a fair and consistent evaluation of the evidence has not been granted to patients with EPP living in England and Wales. Moreover, the IPPN is

concerned about potential equality issues such as the exclusion of patients aged over 70 years from treatment which is not in line with the EU marketing authorisation. Further points concern, for example, the in our assessment unfair pausing of the appraisal during the pandemic, while other appraisals continued, and that the HST committee retrospectively changed the justification for the delays and the narrative of the history of the process.

Therefore, the IPPN would like to appeal against the Final Evaluation Determination for afamelanotide for treating EPP (ID927) on the grounds 1a, 1b and 2, which concerns:

Ground one: In making the assessment that preceded the recommendation, NICE has either:

- failed to act fairly
- exceeded its powers

Ground two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

The individual appeal points are:

1a.1 Pausing the appraisal during the pandemic and further delays in the evaluation of afamelanotide were unfair to patients with EPP in England and Wales
1a.2 It was unfair to not grant access to an executable version of the economic model to the IPPN
1a.3 It was unfair to change the requirements for a managed access agreement between the first and the second FED
1b.1 The Institute has exceeded its powers by retrospectively changing the narrative of the history of the appraisal, i.e., stating a different justification and timeline for pausing the appraisal of afamelanotide
1b.2 The Institute has exceeded its powers by pre-determining the preferred form of evidence for the generation of EQ-5D data as a vignette study
2.1 Using a shorter than usual time-horizon for the economic model was unreasonable given that EPP is a lifelong chronic condition and the

justification for the decision discriminates against patients aged 70 years and older

2.2 It is unreasonable for the committee to assess the EQ-5D feasibility study as less scientifically valid than vignette studies

2.3 It was unreasonable for the committee to not apply a QALY weighting in the case of afamelanotide

The IPPN would like to express their gratitude for the opportunity to bring these points to your attention. Please do not hesitate to contact us in case of inquiries.

Kind regards

[redacted], on behalf of the IPPN

Appendix 1: Barman-Aksözen et al. *in press* (version sent to the Associate Director on 14 February 2023)

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

1a.1 Pausing the appraisal during the pandemic and further delays in the evaluation of afamelanotide were unfair to patients with EPP in England and Wales

The first and second HST committee meeting for afamelanotide for treating EPP [ID927] were held in November 2017 and February 2018. In May 2018, the HST committee issued a negative recommendation for funding of afamelanotide. (NICE 2018, FED ID927) The stakeholders of the appraisal submitted appeals against this recommendation which were upheld in six appeal points on all three grounds for appeal. (NICE 2018 ID927 Appeal Decision) The evaluation was remitted to the HST committee which in March 2019 held a third committee meeting. In March 2020, one year after the third committee meeting, the Evaluation Consultation Document 2 (ECD2) was shared with the stakeholders. However, no closing date for comments was provided (the ECD2 only stated “TBC”). In May 2020, because of challenges associated with the ongoing COVID-19 pandemic, NICE informed the stakeholders via e-mail that evaluations can be defined as being “therapeutically not critical” and that the respective appraisals can be paused. In addition, an update on the NICE website was posted stating that the evaluation of afamelanotide has been defined as therapeutically not critical and that, accordingly, the appraisal was paused. The restart of the appraisal was announced in June 2020 via an update on the website, but no further activities were resumed until February 2022, when NICE organised a virtual stakeholder engagement workshop. In February 2022, a new version of the ECD2 with only minor linguistic changes was shared with the stakeholders who in March 2022 could finally submit their comments. (NICE 2022 ID927 ECD2) In July 2022, the 4th committee meeting was held.

As outlined above, after announcing the restart of the procedure in June 2020, it took NICE over 1.5 years to organise the workshop held in February 2022. However, appraisal procedures for other technologies continued or were even started within this period. This indicates that the committee did have residual capacity to evaluate technologies available despite the challenges caused by the pandemic. At least two of these appraisals (HST19 and HST22) concerned the reassessment of technologies already available to patients in England and Wales (HST2 and HST3, respectively). EPP is associated with severely painful and debilitating phototoxic burn reactions after short exposure times to visible light and far-reaching consequences for all aspects of life. There are currently no treatment options available for patients with EPP living in England and Wales. Principle 8 of the Social value judgements: principles for the development of NICE guidance[1] (NICE 2008) states that: “When choosing guidance topics, developing guidance and supporting those who put its guidance into practice, the Institute should actively consider reducing health inequalities including those associated with sex, age, race, disability and socioeconomic status.” (p. 28) In doing so, NICE should consider, amongst other factors,”The degree of clinical need of patients with the condition or disease under consideration” (p.12). Overall, NICE should seek “to distribute health resources in the fairest way within society as a whole.” (Principle 3, p. 18)

During the Appeal Hearing in 2018, it was established that “EPP very clearly meets the definition of a disability under the Equality Act 2010.” (NICE 2018, Appeal Decision p. 9 ¶ 53). Therefore, the IPPN considers it as unfair that the evaluation of afamelanotide has been defined as therapeutically not critical and was given a lower priority than other appraisals such as the re-assessments of available treatment options, as outlined above. Moreover, the appeal is part of the Accountability for Reasonableness framework which should ensure the fairness in the decision-making process at NICE. The framework consists of the

conditions “publicity, relevance, appeal and revision, and enforcement”. (Schlander 2008) It could be argued that as long as an upheld appeal is not followed by the subsequent steps – that is, revision and enforcement – the fairness of an appraisal proceeding has not been established. (Barman-Aksözen et al. 2022)

In conclusion, the IPPN deems the delays during the pandemic as an unfair act of NICE, given the apparently available residual resources to conduct appraisals during the pandemic and the lack of treatment options for patients with EPP living in England and Wales. Further, the IPPN is concerned about the overall conduct of the procedure with regards to the usually applicable timelines.

Please also see related appeal point 1b.1: The Institute has exceeded its powers by retrospectively changing the narrative of the history of the appraisal, i.e., stating a different justification and timeline for pausing the appraisal of afamelanotide.

Footnotes:

[1] The Guide to the methods of technology appraisal 2013 (issued in 2022) states “The Appraisal Committee will also take into account the Institute's guidance on social value judgements described in the Institute's document, Social value judgements: principles for the development of NICE guidance. This document, developed by NICE's Board, describes the principles NICE should follow when designing the processes used to develop its guidance. In particular it outlines the social value judgements that NICE and its advisory bodies, including Appraisal Committees, should apply when making decisions about the effectiveness and cost effectiveness of interventions.”
NICE (2022): The Guide to the methods of technology appraisal 2013 (PMG9), p.15-16 ¶ 1.4.4). https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (last accessed 22 March 2023) And:
NICE (2008) Social value judgments. Principles for the development of NICE guidance. Second edition
https://pubmed.ncbi.nlm.nih.gov/27905706/ and
https://www.ncbi.nlm.nih.gov/books/NBK395865/pdf/Bookshelf_NBK395865.pdf
(last accessed 18 March 2023)

References:

NICE (2018): Final evaluation document. Afamelanotide for treating erythropoietic protoporphyria
https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document (Last accessed 22 March 2023)

NICE (2018): Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927]. Decision of the panel.
https://www.nice.org.uk/guidance/gid-hst10009/documents/appeal-decision
(Last accessed 19 March 2023)

NICE (2022): Evaluation consultation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: February 2022
https://www.nice.org.uk/guidance/gid-hst10009/documents/evaluation-consultation-document-2 (last accessed 22 March 2023)

NICE (2022): Guide to the methods of technology appraisal 2013 (PMG9).
https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (last accessed 22 March 2023)

NICE (2008) Social value judgments. Principles for the development of NICE guidance. Second edition
https://pubmed.ncbi.nlm.nih.gov/27905706/ and
https://www.ncbi.nlm.nih.gov/books/NBK395865/pdf/Bookshelf_NBK395865.pdf
(last accessed 18 March 2023)

Schlander, M. (2007). NICE accountability for reasonableness: a qualitative study of its appraisal of treatments for attention-deficit/hyperactivity disorder (ADHD). Current medical research and opinion, 23(1), 207-222.
https://www.tandfonline.com/doi/abs/10.1185/030079906X159461

Barman-Aksözen, J., Granata, F., Aksözen, M. H., Dechant, C., & Falchetto, R. (2022). '… they had interpreted "disability" as referring to a patently visible disability': experience of a patient group with NICE. Disability & Society, 37(7), 1239-1245.
https://www.tandfonline.com/doi/full/10.1080/09687599.2022.2060804

1a.2 It was unfair to not grant access to an executable version of the economic model to the IPPN

To understand the economic model and better contribute to the appraisal, the IPPN had repeatedly asked to have access to an executable version of the model. For the current evaluation, amongst other evidence, utility values generated in the EQ-5D feasibility study conducted and submitted by the IPPN had been used. The committee and the evidence review group shared that they had modified the data, such as using age-adjusted utilities. However, the committee did not provide exact information on the adjustments which prevented the IPPN from sufficiently assessing the potential implications.

Since the current QALY calculation was commissioned by NICE and performed by the evidence review group, the IPPN is under the impression that it should have been possible to allow access to the model which unfortunately had not been granted. Access to the model would have enabled the IPPN to contribute more specifically and act proactively to potential flaws in the model. For example, as detailed under point 2.1, questionable justification(s) for the considerably shorter time horizon in the calculation of the QALY gain of afamelanotide were provided by the evidence review group and the committee.

Conclusion:
Access to the model might have put the IPPN in the position to identify and point out such issues beforehand and therefore might have helped to shorten the appraisal time and save resources for all parties involved. The IPPN deems it unfair that access to the model has not yet been granted.

Please see also related appeal point 2.1: Using a shorter than usual time-horizon for the economic model was unreasonable given that EPP

is a lifelong chronic condition and the justification for the decision discriminates against patients aged 70 years and older.

1a.3 It was unfair to change the requirements for a managed access agreement between the first and the second FED

In the Final Evaluation Determination (FED) document for afamelanotide issued in May 2018, two main elements for a managed access agreement (MAA) were detailed by the HST committee: First, data collection to reduce uncertainty at the end of the MAA, and second, a plausible potential for afamelanotide to be considered cost effective. At that time, the committee concluded “that data collection in the context of a MAA was unlikely to resolve the existing uncertainties” and assessed “it highly unlikely that afamelanotide has a plausible potential to be considered cost effective” as the ICER ranged between £1,343,359 and £1,785,957 per QALY gained. (NICE 2018 ID927 FED p. 21-22¶ 4.22)

During the consultation in 2022, the IPPN had submitted the outcomes of their EQ-5D feasibility study, demonstrating amongst other aspects that data collection with this instrument is possible for patients with EPP under long-term treatment with afamelanotide. Further, in the subsequent Evaluation Consultation Document (ECD) issued in September 2022, the committee “considered that these QALY gains, although highly uncertain, were still plausible. This was because they may better reflect the range of patient and clinical expert experiences with the treatment. The committee considered that a plausible ICER was £121,233 per QALY gained because this scenario included its preferred assumptions.” (NICE 2022 ID927 ECD2 p.39¶ 4.58)

Nevertheless, the HST committee in the current FED assessed that “The most optimistic potentially plausible ICER that the committee considered after the third consultation remained in excess of £100,000

per QALY gained, so it concluded that afamelanotide could not be considered for managed access." (NICE 2023 ID927 FED p. 41¶ 4.57) However, according to the currently applicable limit for cost effectiveness, an ICER of £100,000 per QALY gained would be considered cost effective and the technology should be directly recommended for funding.

Conclusion:
The IPPN deems it unfair that the committee apparently changed the requirements for an MAA between issuing the first and the second FED.

References:

NICE 2018: Final evaluation determination – Afamelanotide for treating erythropoietic protoporphyria. Issue date: May 2018 https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document (last accessed 22 March 2023)

NICE 2022: Evaluation consultation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: September 2022 https://www.nice.org.uk/guidance/gid-hst10009/documents/evaluation-consultation-document-3 (last accessed 22 March 2023)

NICE 2023: Final evaluation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: March 2023 https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document-2 (last accessed 22 March 2023)

Ground 1: In making the assessment that preceded the recommendation, NICE has: (b) exceeded its powers

1b.1 The Institute has exceeded its powers by retrospectively changing the narrative of the history of the appraisal, i.e., stating a different justification and timeline for pausing the appraisal of afamelanotide

In May 2020, during the COVID-19 pandemic, NICE announced that evaluations can be defined as being therapeutically not critical and that the respective appraisal procedures can be paused. The stakeholders of the appraisals of afamelanotide were informed about this measure in May 2020 via email. The information that the evaluation of afamelanotide had been defined as being therapeutically not critical and that the appraisal was therefore paused was posted on the webpage on 5 May 2020 in the section “project information” under “timeline”/ “update”. (Figure 1) On 4 June 2020, a new update was posted on the webpage, stating “a phased restart of paused guidance from 01 June” and plans for a virtual stakeholder engagement workshop. However, “the date of the workshop along with further timelines are TBC.” Finally, in December 2021, the information that the workshop was planned for February 2022 was shared with the stakeholders.

Slide 3 of the workshop presentation summarises the history of the appraisal. (Figure 2) Under “ECM3 Mar 2019” it states: “Outcome: not recommended. Appraisal paused to give stakeholders an opportunity to explore further ways to obtain evidence”. However, until this timepoint, the only justification for pausing the appraisal of afamelanotide given by NICE was that the evaluation had been assessed as being therapeutically not critical. Further, the appraisal was not paused after the third committee meeting in March 2019, but in May 2020 during the pandemic. There has been a delay in providing the stakeholders with

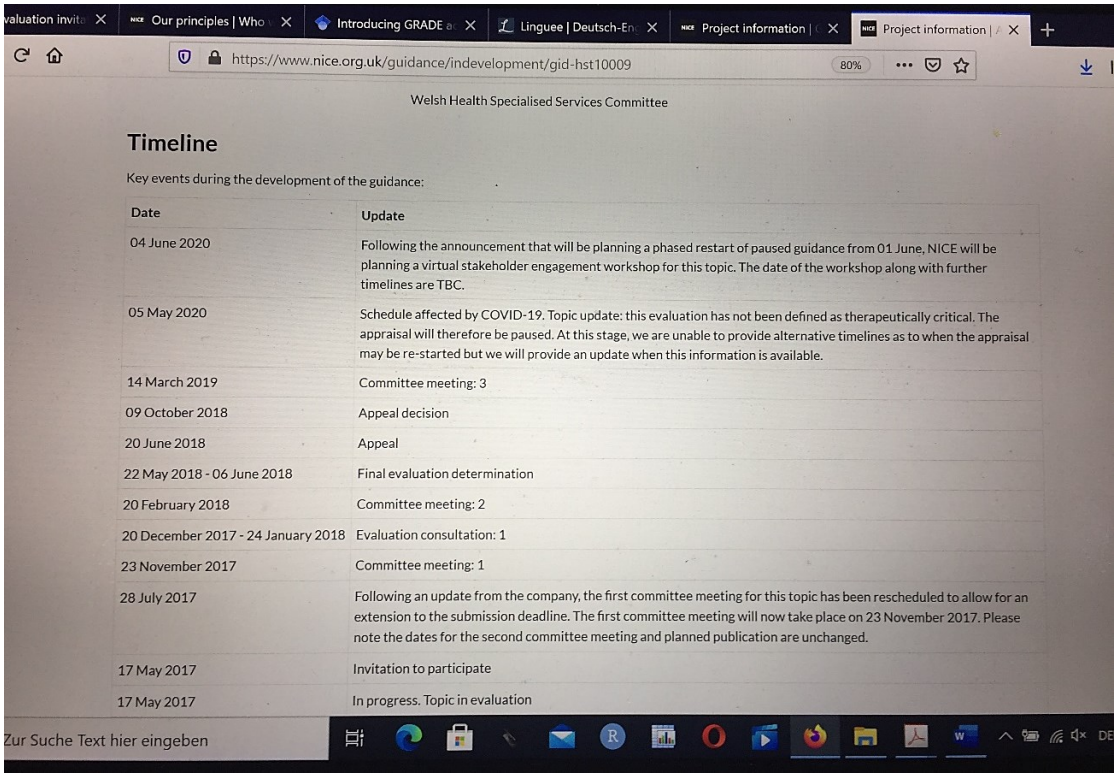
the ECD2 which was shared in March 2020, one year after the third committee meeting. However, the very fact that the EDC2 was produced demonstrates that the appraisal was not paused after the third committee meeting.

At the workshop, the stakeholders, including the IPPN, requested that the depicted history of the appraisal should be corrected, as the provided justification does not accurately reflect the course of the process and has problematic implications: (1) By defining the evaluation as being therapeutically not critical and pausing the appraisal, NICE has potentially acted unfairly towards patients with EPP. (See related appeal point 1a.1) (2) Further, the newly provided explanation that the appraisal has been paused to give the stakeholders an opportunity to explore further ways to obtain evidence incorrectly implies a wider scope of action than given: For example, because the stakeholders did not know how long the pause of the appraisal would be, they were not able to plan larger studies which is time consuming and requires to allocate sufficient resources etc. The pause of the appraisal was communicated in May 2020, and the restart of the appraisals in June 2020. As other appraisals were ongoing / restarted during that time, the IPPN was expecting a timely restart of the appraisal of afamelanotide, too. Stating retrospectively that the pause was to give the stakeholders an opportunity to obtain additional evidence is not only depicting the history of the appraisal incorrectly but implies that the stakeholders did not make good use of the “provided time”. Despite the request of the stakeholders at the workshop to correct the justification for the pause of the appraisal, the slides used for the 4th committee meeting held in July 2022 (slide 7) verbatim remained the same. (Figure 3)
Moreover, meanwhile the homepage has been modified and no longer contains the original statements and timelines: For example, the information provided on 5 May 2020 that the appraisal has been paused is no longer available. A photo of the screen (taken for unrelated reasons in June 2020) with the original information and a

current screenshot from March 2023 are provided below. (Figure 1 and 4)

Conclusion:
Retrospectively changing the narrative of an appraisal does not depict the history of the process in the correct way and therefore does not appear to be within the normal procedures of NICE. Further, the retrospective changes for the justification for pausing the appraisal of afamelanotide and the modification of the timeline are associated with implications for understanding the dynamics of the evaluation process, which the IPPN deems as an unfair approach. NICE must not use their power to modify the narrative of the history of an appraisal process: Since pausing the appraisal of afamelanotide was potentially unfair to patients with EPP, an accurate record of the appraisal process is pertinent not only to the appeal, but also for ensuring trust in the Institution as such.

Please also see related appeal point 1a.1: Pausing the appraisal during the pandemic and further delays in the evaluation of afamelanotide were unfair to patients with EPP in England and Wales.



https://www.nice.org.uk/guidance/indevelopment/gid-hst10009

Welsh Health Specialised Services Committee

Timeline

Key events during the development of the guidance:

Date	Update
04 June 2020	Following the announcement that will be planning a phased restart of paused guidance from 01 June, NICE will be planning a virtual stakeholder engagement workshop for this topic. The date of the workshop along with further timelines are TBC.
05 May 2020	Schedule affected by COVID-19. Topic update: this evaluation has not been defined as therapeutically critical. The appraisal will therefore be paused. At this stage, we are unable to provide alternative timelines as to when the appraisal may be re-started but we will provide an update when this information is available.
14 March 2019	Committee meeting: 3
09 October 2018	Appeal decision
20 June 2018	Appeal
22 May 2018 - 06 June 2018	Final evaluation determination
20 February 2018	Committee meeting: 2
20 December 2017 - 24 January 2018	Evaluation consultation: 1
23 November 2017	Committee meeting: 1
28 July 2017	Following an update from the company, the first committee meeting for this topic has been rescheduled to allow for an extension to the submission deadline. The first committee meeting will now take place on 23 November 2017. Please note the dates for the second committee meeting and planned publication are unchanged.
17 May 2017	Invitation to participate
17 May 2017	In progress. Topic in evaluation

Zur Suche Text hier eingeben

Figure 1. Timelines, dates and updates of the appraisal of afamelanotide for treating erythropoietic protoporphyria [ID927]. Photo of the screen, taken in June 2020.

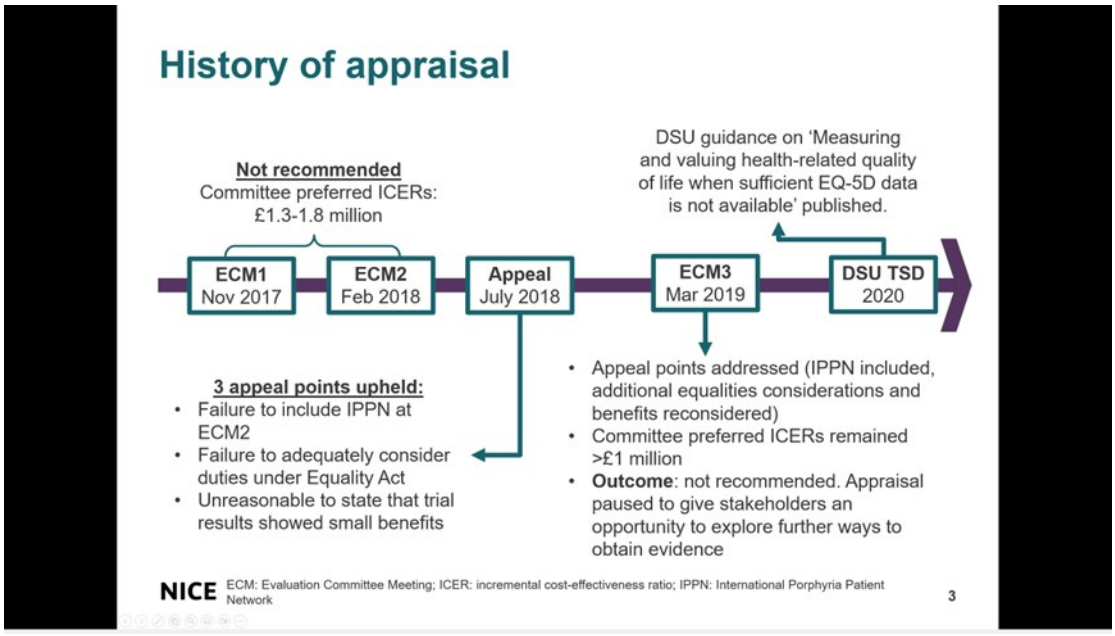


Figure 2: Slide 3 of the presentation held in February 2022 at the stakeholder engagement workshop by the Associated Director of the HST programme.

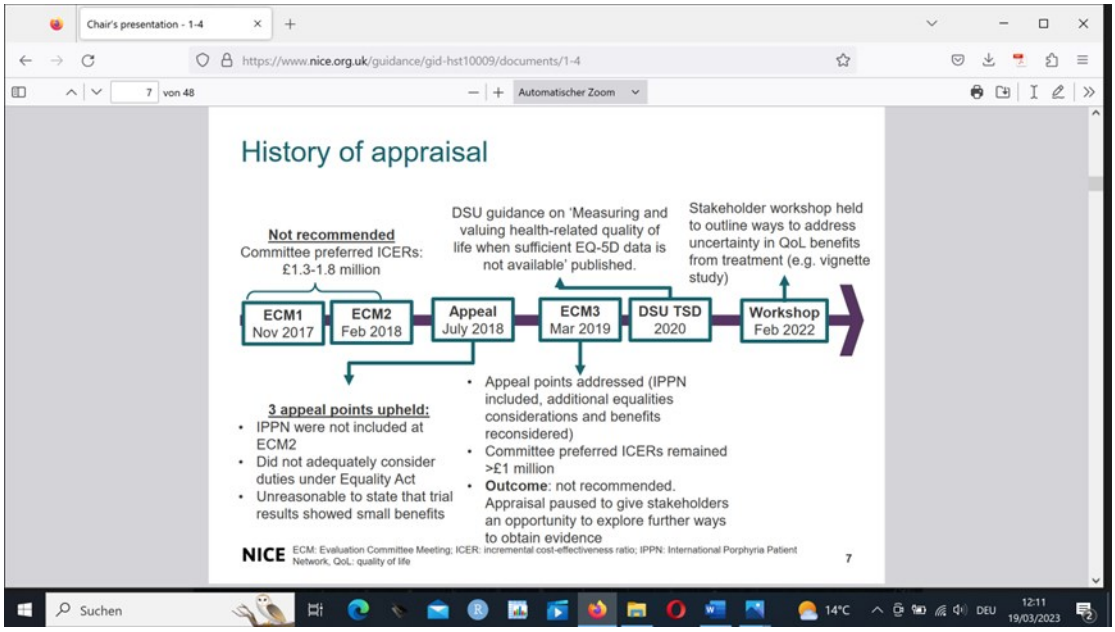


Figure 3: Slide 7 of the presentation held in July 2022 at the 4th committee meeting held by the Chair of the HST committee.

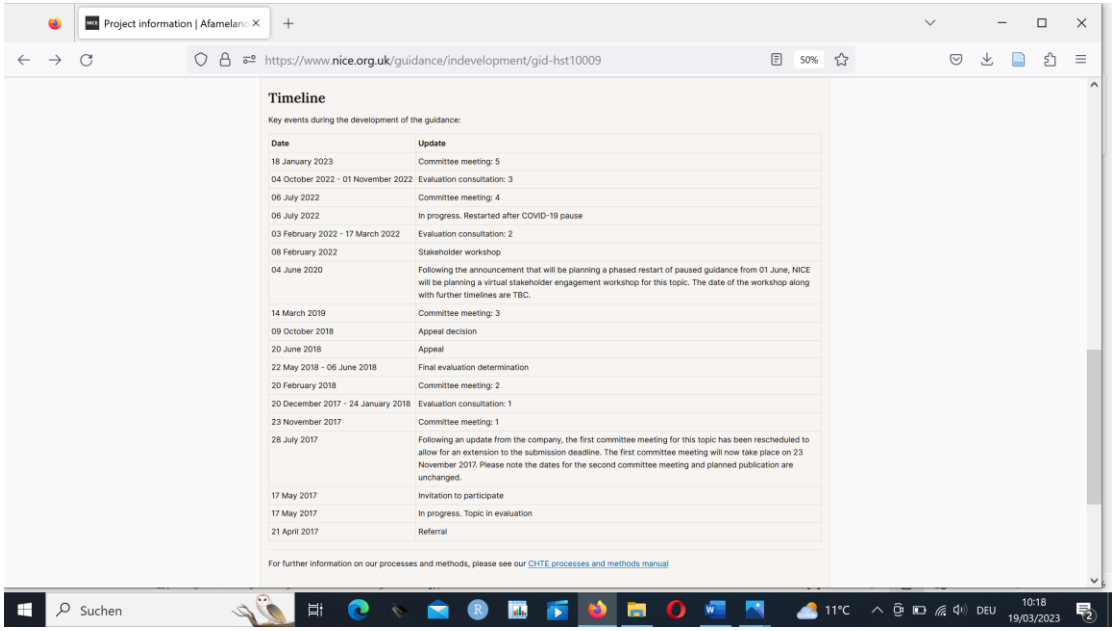


Figure 4: Timelines, dates and updates of the appraisal of afamelanotide for treating erythropoietic protoporphyria [ID927]. Screenshot, taken 19 March 2023

References:

NICE 2022: Stakeholder workshop: Workshop notes Workshop slides (published 10 October 2022): https://www.nice.org.uk/guidance/indevelopment/gid-hst10009/documents

(last downloaded 5 March 2023)

Slides 4th committee meeting 6 July 2022 (published 12 January 2023): https://www.nice.org.uk/guidance/gid-hst10009/documents/1-4 (last accessed 5 March 2023)

1b.2 The Institute has exceeded its powers by pre-determining the preferred form of evidence for the generation of EQ-5D data as a vignette study

A strong preference, or even pressure from the committee towards the conduct of a vignette study was perceptible at the 4th and 5th committee meeting, and is depictable from comments in the FED such as: "[…] the committee was disappointed that the company had chosen not to do a vignette study", and "It [the committee] recalled that the company was not willing to establish a vignette study (see section 4.49) to help quantify the benefits of afamelanotide in terms of QALYs". (NICE 2023, ID927 FED p. 35 ¶ 4.49 and p. 39 ¶ 4.54) Moreover, in the stakeholder briefing document, it is even stated that a vignette study was a condition for a managed access agreement (MAA): "It should be noted that the committee emphasised that a study such as this would be needed in order to reconsider with a greater degree of certainty if afamelanotide would provide value for money (or, if it were to be considered for a managed access arrangement, would have the plausible potential to provide value for money). That is, such a study would be needed before afamelanotide could be considered for a recommendation for routine commissioning or an MAA, and could not be done within an MAA." (NICE 2020, Stakeholder briefing document, p. 5)

The IPPN is under the impression that the demand for a vignette study as the only accepted method to obtain EQ-5D data represents a pre-determination of the outcome that lacks a proper scientific justification. Moreover, it does not appear to be within the normal procedure that a

vignette study was requested as a condition for a managed access agreement, even before the stakeholders were given the opportunity to collect and submit new evidence.

Background:
In March 2020, the committee shared with the stakeholders, amongst other documents, a stakeholder briefing document and a report of the Decision Support Unit named “Measuring and valuing health-related Quality of Life when sufficient EQ-5D data is not available” issued in January 2020 (thereafter: DSU report). The apparent expectation was that the provided information and the DSU report would help the stakeholders to generate evidence more compatible with the evaluation framework preferred by NICE, i.e., the generation of EQ-5D data to calculate Quality-Adjusted Life Years (QALYs). In the stakeholder briefing document, the committee suggested to perform a vignette study to obtain EQ-5D results. After receiving these documents, the IPPN discussed the strengths and limitations of vignette studies in EPP. After careful consideration, the IPPN decided to not perform a vignette study because of reservations regarding their scientific validity in the context of EPP. In what follows, we shortly summarise our reasons for the decision to not perform a vignette study:

(1) The DSU report gives an overview over methods and approaches to obtain EQ-5D data accepted in previous evaluations at NICE, such as vignette studies and proxy conditions utility values, and provides best practice recommendations. As its first key recommendation, the DSU report states: “The use of EQ-5D directly administered to patients and scored using general population preferences is the preferred option to generate utility values. The use of any other method where insufficient evidence cannot be observed remains a second-best alternative, as failure to develop a sufficient body of evidence using EQ-5D, where it would have been desirable and feasible leads to unnecessary uncertainty and incomparability to other appraisals.” (Rowen et al. 2020, DSU report p. 5)

(2) Further, the IPPN in their evaluation of previous appraisals noticed reservations of the Evidence Review Groups (ERGs) regarding vignette studies and that they would have preferred EQ-5D data obtained directly from the patients. One example is from the appraisal of burosumab for treating X-linked hypophosphataemia (HST8): “The committee noted that the utilities were scored by clinicians not patients, and were not taken directly from trials, which were limitations of the data. The vignettes assumed that all aspects of quality of life were worse in more severe health states (that is, there was perfect correlation between RSS and all aspects of quality of life). The ERG explained that asking experts to value the quality of life of hypothetical people is not ideal, and generates results that are substantially uncertain.” (NICE 2018 FED HST8 p.20 ¶4.24)

(3) Most importantly, the IPPN was reluctant about a vignette study because of previous negative experiences with external assessments of EPP disease characteristics. For illustration, during the discussions at the committee meetings the IPPN referred to their previous experience with the Chair of the HST committee during the Appeal Hearing in 2018: “In response to the question “has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?” Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the Act. In response to a request for clarification from the panel, Dr Jackson elaborated by saying that they had interpreted “disability” as referring to a patently visible disability, and that it would be problematic if every disease before them were regarded as a disability. The appeal panel concluded as follows. The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010.” (NICE 2018, ID927 Appeal Decision p. 9 ¶ 51-53) The assessment of the HST committee that EPP would not qualify as a disability because of the alleged absence of visible disease signs (EPP can present with patently visible second degree burn injuries) was put forward by the

Chair of the committee, despite having heard from patients with EPP, their carers, and their medical experts during the scoping workshop and two previous committee meetings, and after having received more than 30 written testimonies from patients during the consultation phase. Moreover, in 2017, the committee had evaluated eliglustat for treating type 1 Gaucher disease (HST5): “The patient experts reported that people with Gaucher disease face the challenge that they usually have no visible disability, except for a few older people who use a wheelchair or walking aids. This can make it difficult for them to access the care, support and services they need, such as benefits and employment support (for example, rest breaks, reduced working hours, time off for appointments and treatment)” (NICE 2017, FED HST5 p.4 ¶ 4.2). In contrast to EPP, the committee had not questioned the status of Gaucher disease as a disability because of the absence of visible disease signs. Because of experiences like the one detailed above, the IPPN was concerned about developing vignettes which, according to the HST committee, should preferably be assessed by members of the general population, i.e., people with even less experience with EPP as compared to the HST committee: “The QoL 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.” (NICE 2023, ID927 FED p.34 ¶ 4.48)

Based on the reasons outlined above, the IPPN decided to not conduct a vignette study. Nevertheless, the IPPN understood the challenge of NICE to evaluate technologies in a consistent manner, which in their framework includes the quantification of health benefits of technologies by QALYs. As no EQ-5D data was available to quantify QALY gains under treatment with afamelanotide and the sensitivity of this generic instrument to disease characteristics and treatment effects had never been investigated, in 2020 the IPPN decided to conduct an EQ-5D feasibility study with a limited number of patients. The IPPN is aware that their feasibility study has several limitations but deemed the

chosen study design, which had been developed together with medical experts in the field, as a scientifically more valid and meaningful approach to collect EQ-5D data for adult patients with EPP than a vignette study. In March 2022, during the consultation phase, the IPPN submitted the results of their feasibility study with the offer to share additional information on the study design etc. Further, in February 2023 the IPPN shared the manuscript of the study with the Associate Director of the HST Programme and members of the staff (annex 1)

On the one hand, in the current ECD (issued in Sep. 2022) the HST committee welcomed the new evidence: “Using the exploratory analyses based on the evidence submitted by the IPPN in the model produced ICERs between £121,233 to £231,320 per QALY gained. These analyses estimated substantially higher QALY gains than those estimated from the clinical trial data. The committee considered that these QALY gains, although highly uncertain, were still plausible. This was because they may better reflect the range of patient and clinical expert experiences with the treatment. The committee considered that a plausible ICER was £121,233 per QALY gained because this scenario included its preferred assumptions.” (NICE 2022, ID927 ECD2 p.39 ¶ 4.58)

On the other hand, the HST committee questioned the decision of the stakeholders to not conduct a vignette study: A strong preference and even pressure from the committee towards the conduct of a vignette study was perceptible at the 4th and 5th committee meeting, which can be also depicted from comments in the FED, such as: “After the second and third consultations, the committee was disappointed that the company had chosen not to do a vignette study”, and “It [the committee] recalled that the company was not willing to establish a vignette study (see section 4.49) to help quantify the benefits of afamelanotide in terms of QALYs”. (NICE 2023, ID927 FED p. 35 ¶ 4.49 and p. 39 ¶ 4.54) In hindsight, a vignette study was already the only option that was presented to the stakeholders at the stakeholder

engagement workshop and in the Stakeholder briefing document issued in March 2020: While the methodology of vignette studies was presented in detail to the stakeholders on the workshop slides, other options, such as utilities from proxy conditions were not even mentioned. (NICE 2022, Stakeholder engagement workshop 8 Feb. 2022, workshop slides 10-12) Utilities from proxy conditions have been accepted in previous appraisals, for example, for the evaluation of givosiran for treating acute hepatic porphyria (HST16) in which utilities from relapsing-remitting multiple sclerosis were used for the calculation of the QALY gain.[1] (NICE 2021, HST16 p.17¶ 4.27)

Because of the perceived strong preference of the committee for a vignette study, the IPPN at the 5th committee meeting asked whether a vignette study conducted in an academic centre and valuated by medical EPP experts (and explicitly not by members of the general population) could be acceptable to the committee. However, the committee did not pay attention to this potential solution and the option was not further discussed. As apparent from the above provided quotes in the FED, it appears that the committee expected the manufacturer of afamelanotide to conduct such a study, not the patient organisations and academic centres. However, the committee needs to explain why they shared documents such as the DSU report with all stakeholders, if the vignette study is supposed to be conducted by the manufacturer? Moreover, what are the reasons of the committee to prefer a vignette study when the DSU report - the very document they shared with the stakeholders - suggests to directly administer the EQ-5D instrument to the patients? Further, the committee should explain why utilities from proxy conditions such as acute burn injuries or chronic neuropathic pain cannot be used for the calculation of the QALY gain, as this approach was apparently acceptable in other appraisals.

Conclusion:

The IPPN considers that the strong preference for a vignette study is a pre-determination of possibly acceptable methods to obtain EQ-5D data by the HST committee that lacks a proper scientific justification. Moreover, it does not appear to be within the normal procedure that a vignette study was requested as a condition for a managed access agreement, even before the stakeholders were given the opportunity to collect and submit new evidence.

Footnotes:

[1] "Overall, the committee concluded that using utilities from relapsing–remitting multiple sclerosis to model the chronic symptoms and from EXPLORE [a natural history study of people with acute hepatic porphyria] to model the acute attacks was reasonable." (NICE 2021 HST16 p.17-18¶ 4.27)
NICE (2021): HST16 Final evaluation document – Givosiran for treating acute hepatic porphyria. Issue date: October 2021
https://www.nice.org.uk/guidance/hst16/documents/final-evaluation-determination-document (last accessed 23 March 2023)

References:

NICE 2023: Final evaluation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: March 2023
https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document-2 (last accessed 22 March 2023)

DSU report (2020): Rowen D, Brazier J, Wong R, Wailoo A. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. NICE DSU Report. 2020.
https://www.sheffield.ac.uk/nice-dsu/methods-development/measuring-health-related-quality-life (last accessed 23 March 2023)

NICE (2018): HST8 Final evaluation document – Burosumab for treating X-linked hypophosphataemia in children and young people. Issue date: August 2018
https://www.nice.org.uk/guidance/hst8/documents/final-evaluation-determination-document (last accessed 23 March 2023)

NICE (2018): Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927].

Decision of the panel
https://www.nice.org.uk/guidance/gid-hst10009/documents/appeal-decision (last accessed 23 March 2023)

NICE (2017): HST5 Final evaluation determination – Eliglustat for treating type 1 Gaucher disease. Issue date: May 2017
https://www.nice.org.uk/guidance/hst5/documents/final-evaluation-determination-document (last accessed 15 March 2023)

NICE 2022: Evaluation consultation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: September 2022
https://www.nice.org.uk/guidance/gid-hst10009/documents/evaluation-consultation-document-3 (last accessed 22 March 2023)

NICE 2022: Stakeholder workshop: Workshop notes Workshop slides (published 10 October 2022): https://www.nice.org.uk/guidance/indevelopment/gid-hst10009/documents
(last downloaded 5 March 2023)

NICE (2021): HST16 Final evaluation document – Givosiran for treating acute hepatic porphyria. Issue date: October 2021
https://www.nice.org.uk/guidance/hst16/documents/final-evaluation-determination-document (last accessed 23 March 2023)

NICE 2018: Final evaluation determination – Afamelanotide for treating erythropoietic protoporphyria. Issue date: May 2018
https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document (last accessed 22 March 2023)

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

As a general consideration, the IPPN would like to point out that since the start of HST Programme in 2013 until now, the same person chaired most of the appraisals and committee meetings. Therefore, a certain degree of consistency between the assessment can be expected.

2.1 Using a shorter than usual time-horizon for the economic model was unreasonable given that EPP is a lifelong chronic condition and the justification for the decision discriminates against patients aged 70 years and older

The currently used time horizon to calculate QALY gains of afamelanotide is 60 years which is considerably shorter than those used in previous assessments. Further, the justifications provided by the committee on why a time horizon of 60 years was chosen are based on unreasonable interpretations of the evidence and regulatory recommendations.

Background:
To better understand the normal procedures and methods of NICE, the IPPN analysed, amongst other aspects, the time horizons used for the economic modelling in previously concluded evaluations of highly specialised technologies. (annex 1) According to the Guide to the methods of technology appraisal 2013 (2022), NICE prefers a “lifetime horizon” for their evaluations. (NICE 2022, p.39¶ 5.1.16) The initial economic model to calculate QALY gains for the afamelanotide treatment had a time horizon of 35 years. (NICE 2017, Committee Papers, p.444) For 18 of the 21 highly specialised technologies with concluded appraisals by December 2022, the time horizon used for the QALY calculation could be identified from the respective appraisal procedure documents.[1] The reported time horizons ranged from 35 to

125 [*sic*] years, with a median of 100 years (mean 81.8 ± 27.5 years). Shorter time horizons corresponded either to diseases associated with a reduced life expectancy or to diseases that only present later in life. Obviously, both reasons do not apply to EPP. Therefore, in their consultation response in March 2022 the IPPN recommended to adjust the time horizon to be more consistent with those used for previously assessed highly specialised technologies. However, the currently used time horizon for afamelanotide is 60 years, which is still considerably shorter than the median 100 years used in other appraisals.

One explanation provided in the FED is that a time horizon of 60 years was chosen because the median age of diagnosis in EPP (and therefore starting age of treatment) would be 22 years, limited data would be available from people aged over 70 and because of specifications in the Marketing Authorisation of afamelanotide as detailed in the summary of product characteristics which would not advise the use of afamelanotide in people over 70. (NICE 2023, ID927 FED p. 32 ¶ 4.44) However, the information about the Marketing Authorisation is incomplete. The summary of product characteristics does not per se exclude patients over 70 years of age from treatment but states: “Since available data in treatment of the elderly are limited, afamelanotide should not be used in patients over 70 years of age. If such patients are treated they must be monitored after administration of every implant, including vital signs, routine haematology and biochemistry.” (EMA 2014, SmPC afamelanotide p.4) In the routine use of afamelanotide, the additional monitoring performed in patients over 70 years comprise the measurement of the blood pressure and the resting heart rate, and the routine blood tests (which are also indicated in patients younger than 70) at least every six months, or as clinically indicated. Therefore, the HST committee considers excluding patients with EPP aged over 70 years from treatment out of trivial reasons. Moreover, the HST committee had peer-reviewed data available from the ongoing PASS which includes patients up to 79 years old. (Wensink et al. 2020)

In previous assessments, the HST committee had accepted time horizons of up to 125 years, “although virtually all patients have died considerably earlier than this point”. (NICE 2013, HST1 ERG report p. 77) In other appraisals, time horizons of 70 years were accepted although the treatment was expected to start later in life. For example, in the appraisal of eliglustat for treating type 1 Gaucher disease (HST5), a time horizon of 70 years was accepted with an expected starting age of treatment between 32 to 38 years. (NICE 2017, FED HST5 p. 14 ¶ 4.29 and 4.31) [2] Therefore, the provided justification to limit the time horizon to 60 years in the case of afamelanotide is not only based on incomplete information and discriminates against patients over 70 years out of trivial reasons but is also not consistent with earlier accepted justifications for time horizons.

Interestingly, in the FED2, a second, alternative explanation for the shorter than usual time horizon is provided: Apparently, the Evidence Review Group had used age-adjustment of utility values for the calculation of the QALY gain of afamelanotide, which leads to higher ICERs when using time horizons longer than 60 years. The reason provided for this modification is that according to the NICE process and methods guide “in some circumstances adjustments to utility values, for example for age or comorbidities may be needed.” (NICE 2023, ID927 FED2 p. 31-32 ¶ 4.44) However, in the case of EPP, life expectancy is normal, and patients aged over 70 years can be treated with afamelanotide as outlined above. Further, comorbidities such as EPP-related liver failure are very rare and can occur at every age. If other circumstances apply which justify age-adjusted utility values in the case of EPP, the committee should have stated them. Moreover, it appears unlikely that using age-adjusted utility values in the way they are currently used in the evaluation of afamelanotide is the normal approach, as otherwise the observed much longer time horizons of median 100 years in the previous HST appraisals are inexplicable.

Why is the IPPN concerned about the shorter than usual time horizon in the case of afamelanotide? Longer time horizons lead to higher QALY gains and can therefore influence the decision-making. In 2017, a modifier (“weighting”) was introduced in the HST programme to reward highly effective treatments: QALY gains between 10 and 30 are multiplied by a factor between 1 to 3. (NICE (2017): Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes) Consequently, higher QALY gains lead to higher willingness to pay-thresholds of up to 300`000 GBP per QALY. The original economic model of afamelanotide had a 35-year time horizon and was submitted by the company before weighting was introduced in the HST programme. However, the calculation of the QALY gain in the current FED was commissioned by the committee and conducted by the evidence review group. Therefore, the evaluating committee would have been in the position to request a time horizon more consistent with the usual approach, especially after having been made aware of the observed differences by the IPPN during the 4th and 5th committee meeting and in written on 14 February 2023, when we shared with the Associate Director of the HST programme and members of the staff a draft manuscript on the matter that we had submitted for consideration for publication to a medical journal (Barman-Aksözen et al. *in press, annex 1).*

Conclusion:
The IPPN considers it unreasonable and unfair that a shorter time horizon is used for the evaluation of afamelanotide than for technologies for the treatment of other chronic conditions with a comparable life expectancy. The shorter time horizon disadvantages patients with EPP as compared to patients with other chronic and lifelong ultra-rare diseases. Moreover, the provided explanation for a shorter than usual time horizon is based on the consideration to exclude patients over 70 from treatment which is not in accordance with the specifications of the Marketing Authorisation of afamelanotide

and therefore discriminates against this subpopulation without a valid reason.

As a side note: Even if the committee is going to prolong the time horizon to a length more consistent with those seen on other chronic, lifelong conditions, it would not, under the current FED, lead to a fairer appraisal. This is so, because the committee also decided not to apply QALY weighting in the case of afamelanotide. This decision contrasts with all other previously concluded appraisals of highly specialised technologies. In fact, with the currently assumed most plausible ICER, if the same rules regarding QALY weighting would have been applied, afamelanotide would be considered cost effective.

See also related appeal point 2.3: It was unreasonable for the committee to not apply a QALY weighting in the case of afamelanotide.

Footnotes

[1] For the remaining three evaluations, only the information that a lifetime horizon had been used was available.

[2] "The starting age of people in the treatment-naive population was assumed to be 32 years based on the mean age in the ENGAGE trial. The starting age of people in the population whose disease was stable with ERT who switched to eliglustat was assumed to be 38 years." (p. 14 ¶ 4.29) "The model used a time horizon of 70 years" (p. 14 ¶ 4.31).
NICE (2017): HST5 Final evaluation determination – Eliglustat for treating type 1 Gaucher disease. Issue date: May 2017.
https://www.nice.org.uk/guidance/hst5/documents/final-evaluation-determination-document (last accessed 23 March 2023)

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NICE (2022): Guide to the methods of technology appraisal 2013 (PMG9). https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (last accessed 22 March 2023)

NICE (2017): Committee papers / Highly Specialised Technology Evaluation Afamelanotide for treating erythropoietic protoporphyria [ID927] Evaluation report. https://www.nice.org.uk/guidance/gid-hst10009/documents/committee-papers (last accessed 23 March 2023)

NICE 2023: Final evaluation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: March 2023 https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document-2 (last accessed 22 March 2023)

EMA (2014): Scenesse. Summary of product characteristics (SmPC): https://www.ema.europa.eu/en/medicines/human/EPAR/scenesse (last accessed 23 March 2023)
"Since available data in treatment of the elderly are limited, afamelanotide should not be used in patients over 70 years of age. If such patients are treated they must be monitored after administration of every implant, including vital signs, routine haematology and biochemistry." (p.4)

Wensink, D., Wagenmakers, M. A., Barman-Aksözen, J., Friesema, E. C., Wilson, J. P., van Rosmalen, J., & Langendonk, J. G. (2020). Association of afamelanotide with improved outcomes in patients with erythropoietic protoporphyria in clinical practice. JAMA dermatology, 156(5), 570-575. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7081144/

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NICE (2017): Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. https://www.nice.org.uk/media/default/about/what-we-do/nice-guidance/nice-highly-specialised-technologies-guidance/hst-interim-methods-process-guide-may-17.pdf (last accessed 4 March 2023)

2.2 It is unreasonable for the committee to assess the EQ-5D feasibility study as less scientifically valid than vignette studies

Background: *(partly overlaps with related appeal point 1b.2, in case appeal point 1b.2 is not going to be part of the final appeal)*
In March 2020, the committee shared with the stakeholders, amongst other documents, a stakeholder briefing document and a report of the Decision Support Unit named “Measuring and valuing health-related Quality of Life when sufficient EQ-5D data is not available” issued in January 2020 (thereafter: DSU report). The apparent expectation was that the provided information and the DSU report would help the stakeholders to generate evidence more compatible with the evaluation framework preferred by NICE, i.e., the generation of EQ-5D data to calculate Quality-Adjusted Life Years (QALYs). In the stakeholder briefing document, the committee suggested to perform a vignette study to obtain EQ-5D results. After receiving these documents, the IPPN discussed the strengths and limitations of vignette studies in EPP. After careful consideration, the IPPN decided not to perform a vignette study because of reservations regarding their scientific validity in the context of EPP. In what follows, we shortly summarise our reasons for the decision not to perform a vignette study:

(1) The DSU report gives an overview over methods and approaches to obtain EQ-5D data accepted in previous evaluations at NICE, such as vignette studies and proxy condition utility values, and provides best practice recommendations. As its first key recommendation, the DSU report states: “The use of EQ-5D directly administered to patients and scored using general population preferences is the preferred option to generate utility values. The use of any other method where insufficient evidence cannot be observed remains a second-best alternative, as failure to develop a sufficient body of evidence using EQ-5D, where it would have been desirable and feasible leads to unnecessary uncertainty and incomparability to other appraisals.” (DSU report p. 5)

(2) Further, the IPPN in their analysis of previous appraisals noticed reservations of the Evidence Review Groups (ERGs) regarding vignette studies and that they would have preferred EQ-5D data obtained directly from the patients. One example is from the appraisal of burosumab for treating X-linked hypophosphataemia (HST8): “The committee noted that the utilities were scored by clinicians not patients, and were not taken directly from trials, which were limitations of the data. The vignettes assumed that all aspects of quality of life were worse in more severe health states (that is, there was perfect correlation between RSS and all aspects of quality of life). The ERG explained that asking experts to value the quality of life of hypothetical people is not ideal, and generates results that are substantially uncertain.” (NICE 2018, FED HST8 p.20 ¶4.24)

(3) Most importantly, the IPPN was concerned about establishing vignettes for a potential vignette study because of previous negative experiences with external assessments of EPP disease characteristics. For illustration, during the discussions at the committee meetings the IPPN referred to their experience with the Chair of the HST committee during the Appeal Hearing in 2018: “In response to the question “has the evaluation committee taken into account any anti-discrimination legislation in coming to its decision?” Dr Jackson replied that the committee did not consider EPP as a disability in the meaning of the Act. In response to a request for clarification from the panel, Dr Jackson elaborated by saying that they had interpreted “disability” as referring to a patently visible disability, and that it would be problematic if every disease before them were regarded as a disability. The appeal panel concluded as follows. The panel took the view that EPP very clearly meets the definition of a disability under the Equality Act 2010.” (Appeal Decision p. 9 ¶ 51-53) The assessment of the HST committee that EPP would not qualify as a disability because of the alleged absence of visible disease signs (EPP can present with patently visible second degree burn injuries) was put forward by the Chair of the committee, despite having heard from patients with EPP, their carers,

and their medical experts during the scoping workshop and two previous committee meetings, and after having received more than 30 written testimonies from patients during the consultation phase.

Moreover, in 2017, the committee had evaluated eliglustat for treating type 1 Gaucher disease (HST5): “The patient experts reported that people with Gaucher disease face the challenge that they usually have no visible disability, except for a few older people who use a wheelchair or walking aids. This can make it difficult for them to access the care, support and services they need, such as benefits and employment support (for example, rest breaks, reduced working hours, time off for appointments and treatment)” (NICE 2017: FED HST5 p.4¶ 4.2). In contrast to EPP, the committee had not questioned the status of Gaucher disease as a disability because of the absence of visible disease signs. Because of experiences like the one detailed above, the IPPN was concerned about developing vignettes which, according to the HST committee, should preferably be assessed by members of the general population, i.e., people with even less experience with EPP as compared to the HST committee: “The QoL 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.” (March 2023, ID927 FED2 p. 34 ¶ 4.48)

Based on the reasons outlined above, the IPPN decided not to conduct a vignette study. Nevertheless, the IPPN understood the challenge of NICE to evaluate technologies in a consistent manner, which in their framework includes the quantification of health benefits of technologies by QALYs. As no EQ-5D data was available to quantify QALY gains under treatment with afamelanotide and the sensitivity of this generic instrument to disease characteristics and treatment effects had never been investigated, in 2020 the IPPN decided to conduct an EQ-5D feasibility study in a limited number of patients. The IPPN is aware that their feasibility study has several limitations, but deemed the chosen

study design, which had been developed together with medical experts in the field, as a scientifically more valid and meaningful approach to collect EQ-5D data for adult patients with EPP than a vignette study. In March 2022, during the consultation phase, the IPPN submitted the results of their feasibility study with the offer to share additional information on the study design etc. Further, the IPPN in February 2023 shared the manuscript of the study with the Associate Director of the HST Programme and members of the staff (Barman-Aksözen et al., *in press,* annex 1)

In the current ECD (issued in Sep. 2022), the HST committee welcomed the new evidence: “Using the exploratory analyses based on the evidence submitted by the IPPN in the model produced ICERs between £121,233 to £231,320 per QALY gained. These analyses estimated substantially higher QALY gains than those estimated from the clinical trial data. The committee considered that these QALY gains, although highly uncertain, were still plausible. This was because they may better reflect the range of patient and clinical expert experiences with the treatment. The committee considered that a plausible ICER was £121,233 per QALY gained because this scenario included its preferred assumptions.” (NICE 2022, ID927 ECD2 p.39 ¶ 4.58)

Arguments specific to this appeal point:

Nevertheless, the committee maintained their position that it would have preferred a vignette study conducted by the manufacturer of afamelanotide. (see related appeal point 1b.2) However, the IPPN deems the design of the EQ-5D feasibility study which had been developed together with medical experts in the field as a scientifically more valid and meaningful approach to collect EQ-5D data for EPP than a vignette study:

Patients with EPP are highly adapted to their condition which makes the quantification of their health related QoL challenging. However, patients under long-term treatment (defined as ≥ two years) with afamelanotide consistently report a self-perceived near-normalisation of all aspects of their daily life and that they almost overcame their ingrained light avoidance behaviour. The IPPN reasoned that, because the EQ-5D is a generic tool, it should be sensitive to long-term treatment effects that lead to a normalisation and cessation of disease specific adaptations. In the presented study, we therefore measured QoL with the EQ-5D and the disease specific EPP-QoL instruments in five patients under long-term treatment with afamelanotide. Moreover, for the study, we selected patients who in addition were affected by an involuntary treatment interruption (caused by a temporary reimbursement suspension), because we hypothesized that individuals who had previously unlearned their adaptation are better able to assess their life without treatment than treatment-naïve patients. The study design was discussed with three independent medical experts in the field and the patients were recruited according to predefined inclusion criteria, including for example the assessment of their emotional stability when confronted with traumatic memories from the treatment interruption time by the retrospective study questions. Patients involved in the design and conduct of the study were excluded as study participants. In our participants, QoL under long-term treatment was comparable to the age-matched population norms. The retrospective results for a treatment interruption and phototoxic reaction time point were comparable to the QoL of patients with chronic neuropathic pain and acute burn injuries, respectively.

The IPPN is aware that the feasibility study has several limitations. However, the strengths of the study and how it compares to evidence for the QALY calculations accepted for previously evaluated highly specialised technologies have in our assessment not been adequately considered by the committee:

- One of the most obvious limitations of our feasibility study is the small sample size of only five participants. However, vignette studies with only four to five medical experts evaluating the different disease states have previously been accepted by the HST committee, for example in the case of HST8. (NICE 2018, HST8 Committee papers, p. 226-227; DSU report)

- Another limitation of our study is that the data for the phototoxic reaction and the treatment interruption timepoints were collected retrospectively. To assess the reliability of the results of the retrospective time points in our cohort, we compared EPP-QoL data collected during the feasibility study with EPP-QoL from the medical records of the participants. Our results suggest that the patients included in our study accurately recalled their QoL for the treatment interruption period.

- Potential selection bias: The patient characteristics data collected for this study suggests that the severity of the disease and extent of treatment benefits seen in the included individuals are within the range that is observed for cohorts from international treatment centres, thus mitigating concerns of an unintentional selection bias of our study cohort.

- Potential response bias: As the included individuals live outside of England and Wales and are currently under treatment with afamelanotide, it was assessed as unlikely that their answers are biased by, for example, the hope to gain access to the treatment.

- No funding from industry: A strength of our study is that it was conducted without funding and influence from industry. To our knowledge, the vignette studies previously accepted by the HST committee were funded by the manufacturers of the respective technologies.

- Relevance of the results: Further, as the study was initiated by a patient organisation (two members are scientists in the field of the porphyrias and one is a medical doctor seeing patients with EPP in her outpatient clinic), aspects relevant to patients with EPP were considered in the design.

In our assessment, the EQ-5D feasibility study represents a new approach to deal with methodological challenges associated with adaptation in rare and chronic diseases. In line with the recommendations of the DSU report, it provides a more reliable estimate of EQ-5D results than using indirect measurements such as utilities from proxy conditions or generated using vignette studies.

The IPPN considers that, in general, evidence should be generated by using the most scientifically valid method and only if expected to provide meaningful results. In our assessment, the evidence for using the EQ-5D instrument in EPP, despite the apparent limitations, is within the range that has been accepted by the HST committee for previous assessments. It should at least allow for a data collection within a managed access agreement.

See also related appeal point 1b.2: The Institute has exceeded its powers by pre-determining the preferred form of evidence for the generation of EQ-5D data as a vignette study.

Footnotes:

[1] "Overall, the committee concluded that using utilities from relapsing–remitting multiple sclerosis to model the chronic symptoms and from EXPLORE [a natural history study of people with acute hepatic porphyria] to model the acute attacks was reasonable." (NICE 2021 HST16 p.17-18¶ 4.27)
NICE (2021): HST16 Final evaluation document – Givosiran for treating acute hepatic porphyria. Issue date: October 2021
https://www.nice.org.uk/guidance/hst16/documents/final-evaluation-determination-document (last accessed 23 March 2023)

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DSU report (2020): Rowen D, Brazier J, Wong R, Wailoo A. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. NICE DSU Report. 2020. https://www.sheffield.ac.uk/nice-dsu/methods-development/measuring-health-related-quality-life (last accessed 23 March 2023)

NICE (2018): HST8 Final evaluation document – Burosumab for treating X-linked hypophosphataemia in children and young people. Issue date: August 2018 https://www.nice.org.uk/guidance/hst8/documents/final-evaluation-determination-document (last accessed 23 March 2023)

NICE 2023: Final evaluation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: March 2023 https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document-2 (last accessed 22 March 2023)

NICE (2018): Advice on Afamelanotide for treating erythropoietic protoporphyria [ID927]. Decision of the panel https://www.nice.org.uk/guidance/gid-hst10009/documents/appeal-decision (last accessed 23 March 2023)

NICE (2017): HST5 Final evaluation determination – Eliglustat for treating type 1 Gaucher disease. Issue date: May 2017 https://www.nice.org.uk/guidance/hst5/documents/final-evaluation-determination-document (last accessed 15 March 2023)

NICE 2022: Stakeholder workshop: Workshop notes Workshop slides (published 10 October 2022): https://www.nice.org.uk/guidance/indevelopment/gid-hst10009/documents (last downloaded 5 March 2023)

NICE (2021): HST16 Final evaluation document – Givosiran for treating acute hepatic porphyria. Issue date: October 2021 https://www.nice.org.uk/guidance/hst16/documents/final-evaluation-determination-document (last accessed 23 March 2023)

NICE 2018: Final evaluation determination – Afamelanotide for treating erythropoietic protoporphyria. Issue date: May 2018

https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document (last accessed 22 March 2023)

NICE (2018): HST8 Highly Specialised Technology Evaluation Burosumab for treating X-linked hypophosphataemia [ID1151] Evaluation report. https://www.nice.org.uk/guidance/hst8/documents/committee-papers (last accessed 23 March 2023)

2.3 It was unreasonable for the committee to not apply a QALY weight in the case of afamelanotide

In 2017, a QALY modifier ("weighting") was introduced in the HST programme to reward treatments associated with "compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained." (NICE 2017, p. 12 ¶53) Consequently, higher QALY gains lead to higher willingness to pay-thresholds of up to 300`000 GBP per QALY.

As detailed in the Evaluation Consultation Document issued in Sep. 2022: "Using the exploratory analyses based on the evidence submitted by the IPPN in the model produced ICERs between £121,233 to £231,320 per QALY gained. These analyses estimated substantially higher QALY gains than those estimated from the clinical trial data. The committee considered that these QALY gains, although highly uncertain, were still plausible. This was because they may better reflect the range of patient and clinical expert experiences with the treatment. The committee considered that a plausible ICER was £121,233 per QALY gained because this scenario included its preferred assumptions." (NICE 2022, ID927 ECD2 , p.39¶ 4.58) Using the preferred ICER of £121,233 per QALY gained from the ECD3, and additional information provided in the appraisal documents of

afamelanotide such as the time horizon, the IPPN was able to estimate an undiscounted QALY gain of 23.796 for afamelanotide (and a 9.995 QALY gain when discounted at 3.5%, respectively). (annex 1)

Because the undiscounted QALY gain of afamelanotide in the scenario that included the preferred assumptions was > 10, a QALY weight should have been applied to afamelanotide. However, the committee "concluded that the criteria for applying a QALY weight were not met" for afamelanotide. (NICE 2023 ID927 FED p. 32 ¶ 4.45) This was, despite in all previous appraisals since the introduction of weighting, a QALY weight was applied in case an undiscounted QALY gain of > 10 was reached. Only in the appraisal of onasemnogene abeparvovec for treating spinal muscular atrophy (HST15) did the committee decide to only apply a partial weighting: "The committee discussed the undiscounted QALY gain associated with onasemnogene abeparvovec and noted it was 18.62 in the scenario considered most plausible (see section 4.35). However, it noted that there was limited long-term effectiveness evidence for onasemnogene abeparvovec and that there were considerable uncertainties in the cost-effectiveness modelling (see section 4.35). To account for these considerable uncertainties, the committee agreed that it would not apply the full QALY weighting of 1.86 but instead would use a lower QALY weighting for its decision making". (NICE 2021 HST15 FED p. 30 ¶ 4.33) The "considerable uncertainties associated with the cost-effectiveness analysis of onasemnogene abeparvovec" were assessed as "likely higher than levels typically seen in treatments evaluated through the highly specialised technology programme." (NICE 2021 HST15 FED p.31¶ 4.35) and comprised, amongst other things, the small numbers of trial participants (n=34), uncertainty resulting from the use of natural history studies conducted in the US, insufficient long-term evidence, lack of evidence for patients older than 6 months at treatment administration, lack of data of the amount of care needed after treatment and use of utilities from a proxy condition. (NICE 2021 HST15 FED p. 31-33 ¶

4.35) Nevertheless, the committee decided to at least apply a partial QALY weighting in the case of HST15.

When comparing the circumstances for applying at least a partial QALY weight in the case of HST15, it appears unreasonable that the committee in the case of afamelanotide decided to not apply a QALY weight at all. According to the “Guide to the methods of technology appraisal 2013”, “the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals.” (p. 71¶ 6.2.15) The IPPNs considers that this should include that the “uncertainty” of the treatment benefits is assessed by the same standards. The utility values used for the calculation of the QALY gain of afamelanotide were obtained by directly administering the EQ-5D instrument to patients which according to the DSU report is the preferred method, the preferred ICER is close to the cost effectiveness threshold (even when using the updated list price which results in an ICER of £133,748 per QALY gained. (NICE 2023 ID927 FED2 p.37 ¶ 4.51) The pivotal trial testing afamelanotide is an RCT (n=93) with statistically significant results for the primary endpoint (Langendonk et al. 2015) Long-term treatment experience of up to 12 years is available from peer-reviewed publications from several countries. (Biolcati et al. 2015) Further, new endpoints demonstrating maximum sunlight exposure times under treatment of approximately 3 hours, treatment adherence ranges between 93% to 98% and assessments of clinical experts confirm the effectiveness and the benefit the treatment provides. (Barman-Aksözen et al. 2020, Wensink et al. 2021; Leaf & Dickey 2023) In 2019, the EMA, based on safety and efficacy results measured in the mandatory post-authorisation safety and efficacy study (PASS), confirmed the initial marketing authorisation of afamelanotide.[1] (Wensink et al. 2021) Further, in 2021, Germany confirmed their positive recommendation for funding based on the PASS data, etc. etc. Taken together, the body of evidence for the quality and quantity of the treatment benefits of afamelanotide exceeds that of HST15 and that of many previously

assessed technologies, which were all assessed as suitable for weighting if associated with an undiscounted QALY gained of > 10.

Moreover, the calculation of the QALY gain of afamelanotide was already affected by the unreasonable short time horizon of 60 years when compared to the median 100 years as accepted for other highly specialised technologies and the application of age adjustment of the utilities which does not appear to be the normal approach. (see appeal point 2.1). Despite these “punishments”, an undiscounted QALY gain > 10 was achieved which should have made afamelanotide eligible for weighting.

The IPPN considers it as unreasonable for the committee to not apply a QALY weight in the case of afamelanotide and as an inconsistent and unfair approach.

Footnotes:

[1] “Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of SCENESSE in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity” (EMA 2019, SCENESSE Procedural steps taken and scientific information after the authorisation SmPC, Annex II and PL). EMA 2019. https://www.ema.europa.eu/en/documents/procedural-steps-after/scenesse-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf

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NICE 2022: Evaluation consultation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: September 2022

https://www.nice.org.uk/guidance/gid-hst10009/documents/evaluation-consultation-document-3 (last accessed 22 March 2023)

NICE 2023: Final evaluation document 2 – Afamelanotide for treating erythropoietic protoporphyria. Issue date: March 2023 https://www.nice.org.uk/guidance/gid-hst10009/documents/final-evaluation-determination-document-2 (last accessed 22 March 2023)

NICE (2021): HST15 Onasemnogene abeparvovec for treating spinal muscular atrophy. Issue date: May 2021 https://www.nice.org.uk/guidance/hst15/documents/final-evaluation-determination-document (last accessed 23 March 2023)

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Conclusion

Out of the points detailed in this appeal document, the IPPN concludes that the HST committee in preparing the current FED had acted unfairly towards patients with EPP, has exceeded its powers and interpreted the provided evidence for the effectiveness and benefit of afamelanotide in an unreasonable way. Further, in the assessment of the IPPN, the HST committee has not sufficiently addressed the appeal points upheld in the last Appeal.

Because of the complexity of the appraisal, the IPPN deems an oral appeal hearing as a more suitable format.