NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Afamelanotide for treating erythropoietic protoporphyria [ID927]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Company comments on the Evaluation Consultation Document** from Clinuvel

3. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - **British Porphyria Association**
   - **International Porphyria Patient Network (IPPN)**
   - **British Association of Dermatologists (BAD)**

4. **Comments on the Evaluation Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	CLINUVEL	Section 1.2 *"There is some evidence from clinical trials that afamelanotide provides benefits for people with EPP".* Why does NICE choose to qualify this sentence with the use of the word "some"? This wording is not used in any other HST process to describe evidence from clinical trials. The statement is a definitive one – there either is, or is not, evidence from clinical trials of the benefit of afamelanotide to EPP patients. The Committee has previously been found by NICE's appeal panel that describing the effect of treatment as "small" is unreasonable. Deliberately chosen wording aims to shed doubts about efficacy, while prescribers and patients have used the drug without interruption for 8 years now under conditions of use, and 16 years including all clinical trials and compassionate use. 'People with EPP' is a lay term for patients lifelong affected by a disease poorly characterised.	Thank you for your comments. "Some" has been used because, as pointed out by the company, there was a lack of scientific tools to capture the true impact of EPP and the benefit of afamelanotide (section 4.13). The document has been written in line with the NICE style guide. Please see section on 'talking about people' for further detail.
2	Company	CLINUVEL	Section 2.1 *"caused by sunlight and some types of artificial light… sunlight avoidance"* Evidence provided to the Committee from multiple sources during the various consultations on this evaluation is that it is specific wavelengths of light along the visible spectrum – the Soret band, peaking at 408nm – which causes phototoxicity in EPP. More accurate phrasing would be "caused by light sources, both sunlight and artificial light emitted specifically along the visible spectrum above 400 nm" and "sun and generally, light avoidance".	This has been updated in the FED (section 2.1).
3	Company	CLINUVEL	Section 3.2 A broader safety profile than that seen in clinical trials is now taken into account as part of the summary of product characteristics.	A link to the summary of product characteristics is provided in the FED and the section has been updated to remove this list (section 3.2).
4	Company	CLINUVEL	Section 3.3	The FED has been updated to reflect the new list

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			"Afamelanotide has not been launched in the UK, but the company has stated that the cost of an implant will be £12,020 (excluding VAT)." SCENESSE® has been launched in the UK and is prescribed to patients in Scotland under a patient access scheme. The approved NHS list price of the medication is £13,209 (ex VAT). The Company has notified NICE of the UK launch and Scottish program on a number of occasions, including at the 8 February 2022 Workshop, at Committee meeting 4 on 6 July 2022, on a call with the CEO of NICE on 26 July 2022, and in correspondence on 16 March 2022 and 14 July 2022.	price.
5	Company	CLINUVEL	Section 4.8 *"…the specific challenge in measuring the effect of the condition and its treatment on quality of life… It heard that there was an important lack of robust scientific instruments to measure such effects."* The EMA's opinion on scientific instruments – as presented to the Committee by the Company over six years – relates not only to the impact on patient QoL, but also more broadly to the overall impact of the disease and the Company's ability to generate data on efficacy and clinical benefit as per the EMA's outcome. While QoL may be the focus of section 4.8, this broader effect and finding is relevant to the overall assessment made by NICE.	The FED has been updated to reflect this (section 4.8).
6	Company	CLINUVEL	Section 4.18 *"The company stated that it had consulted with EPP experts to develop the EPP-QoL. However, it was unable to provide the committee with a response to whether it had used standard methods for developing and validating this tool."* This statement is factually incorrect and contradicts the later statement that a peer-review publication validating the EPP-QoL that was provided to the Committee. The ECD is not written in a manner which reflects the chronological interactions on the review of afamelanotide, so it is unclear why statements such as the above remain. If a chronological representation of the review would have been made, then the ECD would not have omitted salient points, including all matters relating to the appeal panel (which is not mentioned at all, despite the Committee being found, for example, to	This statement has been removed to make it clear that the EPP-QoL has now been partially validated (section 4.18). This is an editorial issue. ECDs are usually written based on the grouping of relevant themes rather than in a manner which reflects chronological interactions.

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			have breached the Equality Act, 2010), contradictions on the use of qualitative data (as outlined in correspondence to NICE on 16 March 2022 and 14 July 2022 and discussed below) and the unexplained delays in the review process between the third Committee Meeting in 14 March 2019 and the "Stakeholder workshop" of 8 February 2022. The ECD intentionally cherry picks its arguments while omitting significant parts of the Company's arguments, as found back in the minutes and outcome of the Appeal Panel, July 2018. Further, it is unclear why the first sentence – which references the Company's undisputed work with EPP experts to develop the EPP-QoL – should be followed by a contradictory "however", which suggests that all work and expertise around the EPP-QoL should be questioned. The persistence of this approach is unreasonable and misleads the reader.	
7	Company	CLINUVEL	Section 4.19 *"The committee noted that, in a large observational study, DLQI had been shown to be sensitive to the effect of EPP on people with the condition…* *The committee concluded that, although DLQI had notable limitations, it had been one of the tools incorporated in the clinical trials at the outset to measure QoL and the results were relevant to its consideration of clinical effectiveness."* There is an inconsistency in the acceptance of evidence by the Committee. It is assumed – although this is not stated – that the study referenced is Holme et al (2006), which uses the DLQI in a cohort of UK EPP patients. A more recent UK study – Jong et al (2009), which was also submitted to the Committee, involves most of the authors of the 2006 study and is co-authored by both of the clinical expert stakeholders – recognised the challenges of studying photodermatoses and EPP and adapted the DLQI to include a longer recall period, as "a short time base of 1 week may 'miss' the QoL impact" in a disorder with intermittent symptoms and as no photodermatoses-specific QoL has been published. Rutter et al (2019) – also submitted to the Committee and co-authored by one of the clinical expert stakeholders – discusses these challenges in further detail.	As stated by the ERG, Jong et al. (2008) and Rutter et al. (2020) do not contradict the statements in the ECD. Both papers critically discuss the sensitivity of the DLQI in EPP, citing advantages and disadvantages of this measure (section 4.19).

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			The Company has made considerable submissions to the Committee outlining the inappropriate nature of the DLQI for capturing disease benefit in EPP. Most importantly, the EMA had, in its review, accepted that the DLQI is not an appropriate tool for measuring the impact of disease and therapy in EPP, nevertheless the Committee persists in its arguments. The medical community of experts is no longer using the DLQI in EPP or most severe photodermatoses.	The committee concluded that, although DLQI had notable limitations, it had been one of the tools incorporated in the clinical trials at the outset to measure QoL and the results were relevant to its consideration of clinical effectiveness (section 4.19).
8	Company	CLINUVEL	Section 4.24 *"[the Committee] also highlighted that it considers qualitative evidence as part of its careful deliberation on all the factors that have contributed to its conclusion. For example, it contributes to the understanding of the nature of the condition, and to interpreting the clinical evidence. 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."* The Company welcomes the Committee's recognition that qualitative evidence has been, and should further be, taken into account in the context of this evaluation. However, in this context it is erroneous for the Committee to criticise qualitative evidence submitted by CLINUVEL, patient groups and other stakeholders without noting that the Committee's current position contradicts earlier advice provided to the Company in the February 2020 and February 2022 draft ECDs – as highlighted in correspondence to NICE on 16 March 2022, 14 July 2022 and during the fourth Committee meeting on 6 July 2022 – which stated: *"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*	

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			analysis" As outlined above, if the ECD is to follow a chronological review of afamelanotide, this salient point should be reinstated, along with the formal response by the Committee chair during Committee meeting 4. It is further unclear to the Company why the draft February 2020 and February 2022 ECDs were never finalised or published by NICE.	This previous statement concerning qualitative evidence has been updated with a statement that more clearly reflects committee's views (section 4.23). The second ECD developed following the March 2019 ECM was released to the company and stakeholders only - no formal consultation took place after ECM3. Therefore, it was not added on the NICE website. It was re-released for formal consultation in March 2022. This is now on the NICE website.
9			Section 4.30 *"The ERG said that there was substantial uncertainty over the results. They have wide confidence intervals and there are limitations in reporting."* The Company notes that Wensink et al (2020) is the largest single cohort study of EPP ever published. It is unclear why the ERG's approach to this article – which is peer reviewed and published in *JAMA Dermatology* – is not more closely reviewed by the Committee as to whether it is a reasonable interpretation. Rather, the ERG's comments appear to be taken at face value and without critique. It is important to state that the Company is not involved in the publication of results as submitted by expert clinicians, and that editorial input is not provided.	As per the FED, the ERG maintained its conclusions, in the absence of any alternative critical interpretation of Wensink et al. (2020) provided by the company (section 4.29).
10	Company	CLINUVEL	Section 4.30 *"Barman-Aksözen et al. (2020)…..People having afamelanotide"* The terminology is odd and demonstrates lack of professionalism in dictum. We suggest "receiving treatment with afamelanotide" would be more appropriate.	The document has been written in line with the NICE style guide.
11	Company	CLINUVEL	Section 4.30 *"Wensink et al. (2021)……The ERG again noted a lack of clarity in the study over participant recall. It also pointed out that the instrument used to measure results had not been validated."* The Company agrees that this study, whilst interesting, has limited value	Comment noted, no action required

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			in evaluating the impact of EPP on patients' quality of life and the effectiveness of treatment. The endpoint "time to prodrome" measures a subjective exposure time until patients experience a "warning" signal, but there is no data to support its use in evaluating disease impact or clinical benefit. While prodromes are a unique feature of EPP, their relationship to the length and severity of phototoxicity in EPP is not defined and to suggest a direct relationship between the onset of the prodromal phase and symptoms ignores the unique nature of the disease.	
12	Company	CLINUVEL	Section 4.30 *"The ERG said Minder et al. study results may have suggested positive results in relation to liver damage. But it added that, in clinical practice, tests other than those used in the study are likely to be used to assess liver damage."* The ERG's conclusions are factually incorrect and indicate a complete lack of understanding of clinical care and monitoring in EPP. PPIX and AST are primary biochemical markers of liver function in EPP patients and are used in routine UK and EU clinical practice to monitor for potential liver damage. Both of these markers are reported in the Minder et al. study, along with 13 other laboratory measures. Considerable evidence of the use of AST and PPIX levels to monitor liver function has been included in Minder et al., as well as publications submitted throughout the evaluation of afamelanotide. Based on the evidence submitted, it is unreasonable for the Committee to include such commentary from the ERG without adequate assessment and critique.	As per the FED, the ERG stated that it was unclear why standard liver function tests such as ALT and bilirubin were not also done to provide a more complete picture of liver health, given that the focus of interest in the study is detecting the presence of absence of liver damage. It added that the 13 other laboratory measures referred to by the company do not include any liver-specific markers (section 4.29). The committee papers presented to the committee include the stakeholder responses, which present the clinical data, as well as the ERG review of the data. The committee deliberate on the evidence presented and take account of all available evidence in their decision-making process.
13	Company	CLINUVEL	Section 4.40 *"The committee noted that the modelling was based on EPP-QoL data collected at 4 months, but that this data was also collected at 6 months, although from a smaller proportion of the trial population. This data had not been presented by the company. The committee considered that, if the EPP-QoL data was to be used, the longer follow-up data could have been useful to see. This was particularly because 1 clinical expert explained that the benefits of afamelanotide may take time to become*	

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			apparent if people adapt their conditioned behaviour gradually" The Company notes that considerable QoL data from the use of the EPP-QoL has been made available to the Committee over the course of **the six year** review by the Committee, including long-term use in the Wensink et al (2020) and Minder et al (2021) studies, as well as the validation study (Biolcati et al, 2021). As a result, such a comment is not only unreasonable, in light of the evidence presented, but now also factually incorrect. As highlighted above, the Committee's omission to present a chronology breakdown of the review of afamelanotide leads to an ECD lacking detail and context.	This statement refers specifically to the company's trials in which EPP-QoL was assessed at 180 days (6 months) follow-up but results in the company submission were provided only up to 120 days (4 months) The ERG requested the 180 day follow-up data from these three trials in a clarification question to the company but the company did not provide these data in their response.
14	Company	CLINUVEL	Section 4.48 *"Before the second consultation the committee explored ways to quantify the health benefits described by patients' and clinical experts' testimonies in terms of QALYs. It suggested that utility scores for the economic model could be estimated through an indirect method such as a 'vignette' study."* Section 4.49 *"After the second consultation, the committee was disappointed that the company had chosen not to do a vignette study."* The Company has responded extensively to the Committee's requirement for a vignette study, as the only method by which new data can be evaluated for the review of afamelanotide and has explained in detail why we consider the Committee's position to be unreasonable and unfeasible. The publication of the ECD in the absence of the Company's response is unbalanced and we ask NICE to publish this correspondence as a matter of transparency. We note that vignettes feature heavily in the ECD, despite no evidence from the Committee that this methodology is suitable for use in EPP (it has not, for example, been validated for the disease, a major critique of the Committee and ERG of other tools presented to the Committee). The Company's position, as provided to NICE by letter dated 14 July 2022, is as follows:	The committee considered that quantifying the effects of the condition and benefits associated with afamelanotide, and translating those into QALYs, was a crucial uncertainty in the economic modelling (section 4.38). The committee explored ways to quantify the health benefits and explained how a vignette study could be utilised (sections 4.48 and 4.49). The committee noted that similar approaches had previously been considered in other highly specialised technologies evaluations when direct measurement was not possible, as recommended by the decision support unit

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			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	guidance on the use of qualitative evidence to inform generation of utility values in health technology assessment (section 4.49). The committee also considered other approaches that could be used to quantify health benefits. While the vignette study remained the committee's preferred method for the quantification of QALYs, it accepted that alternative approaches like those proposed by the company in the managed access agreement proposal could also generate utility values (section 4.56).

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			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	

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			these remain valid, even though they have been rejected by NICE's executive in previous appeal processes. Importantly, the Company's concerns and the issues raised in our letter of 14 July 2022 have not been answered of explained by NICE or the Committee either in correspondence, discussion or in the ECD.	
15	Company	CLINUVEL	Section 4.51 *"It recalled that it decided not to apply a QALY weighting (see section 4.44, and noted that the plausible ICER was above what could be acceptable for a highly specialised technology."* There is a typographical error in this sentence.	Comment noted
16	Company	CLINUVEL	Section 4.53 *"The committee would welcome a new proposal for managed access from the company, including a data collection proposal and commercial access proposal, to explore whether a managed access agreement for afamelanotide would be feasible."* **Managed access agreement proposals submitted** The Company submitted a proposal for a managed access agreement prior to receipt of the ECD draft, as well as submitting a proposed managed access agreement in 2018, and requesting to submit or discuss managed access agreements in correspondence on 8 March 2019, 20 January 2020 and 14 July 2022, and at meetings on 11 June 2021, 8 February 2022 and 26 July 2022. The Company most recently discussed a possible managed access agreement with NICE on 19 August 2022. At this time, NICE suggested that a draft ECD would be received within 2-3 weeks, with which the Company could refine a managed access agreement proposal. After receiving no correspondence for more than one month, the Company submitted a proposal for a managed access agreement on 21 September 2022. Access to the draft ECD was only granted by NICE on 27 September 2022. Despite its best efforts to engage on a data collection agreement, the Company takes this opportunity to provide further context to the proposed managed access agreement and data collection proposal it has outlined.	The committee considered the managed access agreement proposal (sections 4.54- 4.57).

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			Direct, quantitative approach to data collection The Company considers that only a direct quantitative approach, based on validated, disease-specific tools, and which incorporates analyses of long-term data captured in England and similar countries is appropriate for a data collection under a proposed managed access agreement. This will allow for a more informed decision to be made about patient access and long-term NHS funding, as well as the viability of supplying SCENESSE® to the UK post-Brexit. Such an approach also best aligns with NICE's preferred methods for technology appraisal/evaluation for a patient population in which no further randomised controlled trials can ethically be conducted, and minimises the overall burden on patients and NHS staff asked to collect data. CLINUVEL proposes a Data Collection Agreement which: • Recognises that standard HRQoL methods are inappropriate for EPP, in part due to reasons consistent with findings of the European Medicines Agency (as set out in the European Public Assessment Report) • Uses disease specific tools already in clinical use across Europe, with efforts focused on validating and mapping these to accepted HRQoL tools and measures. • Accepts data from the ongoing post authorisation safety studies, real world evidence generated since 2016, consistent with the approach agreed during Committee Meeting 4 on 7 July 2022 • Incorporates disease specific tools developed to capture impact on patient QoL as well as overall disability (Inventory of Daily Activities). **Disease-specific tools** The Committee has repeatedly expressed concerns in relation to "uncertainties" around measures used in evaluation of EPP and afamelanotide, with a particular focus on the EPP Quality of Life (EPP-QoL) tool. For example, 4.18 of the ECD notes "The committee was also aware that the EPP-QoL had not been assigned preference weights and had not been mapped to an outcome measure that could provide preference weights. This meant that the measure could not be used to generate utility values". In order to address this, rather than seek to pursue methodologies which have no proven validity in EPP patients, the	

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			Company intends to work with existing tools for which extensive data are available. There is an extensive body of data from the use of the EPP-QoL, with the tool first deployed in clinical trials and subsequently used over [redacted] times with patients post-authorisation. A partial validation of the tool has been completed (Biolcati et al., 2021). In parallel, alongside EPP experts, CLINUVEL has developed an EPP-specific Inventory of Daily Activities (IDA) tool, which has been in use post-authorisation since 2016. The IDA seeks to capture information on the overall disability and restrictions placed on EPP patients, and changes to these over time. CLINUVEL proposes to further the use of the EPP-QoL – as submitted annually to the EMA and FDA - and IDA to exhaustively determine whether these can be mapped to HRQOL measures and tools. The proposed five year window for data collection and analysis is expected to provide time to capture sufficient English data (along with that already captured in Europe and Scotland) and implement the most appropriate approach. Up to twenty percent of EPP patients experience liver injury, with four percent suffering terminal liver failure requiring a life-saving transplantation. Recently published data (Minder et al., 2021) suggests that long-term treatment with SCENESSE® may have a hepatoprotective effect in EPP patients. CLINUVEL is investigating this new finding to determine whether similar outcomes are seen in the broader EPP patient cohort. If confirmed, the Company would seek to incorporate such an outcome in its data collection and evidence base. **Method of data capture – real world evidence** CLINUVEL has established the largest EPP disease registry, the European EPP Disease Registry or EEDR, data from which have already been accepted by NICE as part of the second consultation process. The Company proposes to extend the use of the EEDR into England to capture data on real world use of SCENESSE®, including the number of implants received per patient per annum, and deploying the EPP-QoL and IDA tools. Further measures on patient safety and treatment	

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			compliance – as previously provided to NICE – are also captured in the EEDR. The Company completes annual analyses of EEDR data, copies of which are provided to regulatory authorities (EMA, MHRA, FDA). **Commercial proposal** CLINUVEL has been advised by NHS England (9 November) that it has been unable to schedule a discussion on a commercial proposal between the Company, NHSE and NICE until 15 December 2022, after the closing of the consultation period; this had not previously been communicated to the Company. Consistent with the Company's transparent approach to pricing and uniform pricing policy (and the Scottish PAS), CLINUVEL would make SCENESSE® available at the uniform price to NHS England, recognising that it is more than six years since this price was first offered to the NHS and that no English EPP patients have received treatment coverage to date. The Company has already stated that it will commit to the principles of the Innovative Medicines Fund, should this be the pathway pursued by NHS England for SCENESSE®. **Timelines** Based on a proposed HST meeting in January 2023, CLINUVEL would be able to implement the proposed data collection plan in time for Spring 2023 in England, pending agreements with the few English centres willing and able to treat EPP patients.	
17	Company	CLINUVEL	**References** Biolcati, G., Hanneken, S., Minder, E. I., Neumann, N. J., Wilson, J. H. P., Wolgen, P. J., Wright, D. J., & Lloyd, A. J. (2021). Validation of a novel patient reported tool to assess the impact of treatment in erythropoietic protoporphyria: The EPP-QoL. Journal of Patient-Reported Outcomes, 5(1), 65. https://doi.org/10.1186/s41687-021-00345-7 Holme, S. A., Anstey, A. V., Finlay, A. Y., Elder, G. H., & Badminton, M. N. (2006). Erythropoietic protoporphyria in the U.K.: Clinical features and effect on quality of life. British Journal of Dermatology, 155(3), 574–581. https://doi.org/10.1111/j.1365-2133.2006.07472.x	No action required

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			Jong, C. T., Finlay, A. Y., Pearse, A. D., Kerr, A. C., Ferguson, J., Benton, E. C., Hawk, J. L. M., Sarkany, R. P., McMullen, E., Rhodes, L. E., Farr, P. M., & Anstey, A. V. (2008). The quality of life of 790 patients with photodermatoses. The British Journal of Dermatology, 159(1), 192–197. https://doi.org/10.1111/j.1365-2133.2008.08581.x Minder, A.-E., Barman-Aksoezen, J., Schmid, M., Minder, E. I., Zulewski, H., Minder, C. E., & Schneider-Yin, X. (2021). Beyond pigmentation: Signs of liver protection during afamelanotide treatment in Swiss patients with erythropoietic protoporphyria, an observational study. Therapeutic Advances in Rare Disease, 2, 263300402110654. https://doi.org/10.1177/26330040211065453 Rutter, K. J., Ashraf, I., Cordingley, L., & Rhodes, L. E. (2019). Quality of life and psychological impact in the photodermatoses: A systematic review. The British Journal of Dermatology. https://doi.org/10.1111/bjd.18326	
18	Professional organisation	British Porphyria Association	We are pleased that the additional evidence has been taken into account in the ECD 3, and pleased that the ICER is dramatically closer to the ICER threshold than it was in ECD 1 or 2. As a patient group, however, we are disappointed that a positive recommendation for routine use wasn't possible, though we are hopeful that the company, NHS England and NICE may be able to come to some arrangement to provide the medication under a Managed Access Agreement via the Innovative Medicines Fund. The body of evidence that Afamelanotide is a highly effective treatment for patients who do have access to it continues to grow. We therefore urge the company and NICE to find a way of working together more effectively, in order to close the remaining gap and get this medication to patients.	Thank you for your comments. The committee considered the company's managed access agreement proposal and acknowledged the launch of the IMF fund (sections 4.54- 4.57).
19	Patient organisation	The International Porphyria Patient Network (IPPN)	**Executive summary:** The IPPN appreciates that much of the submitted evidence has now been taken into account and that the understanding of the committee regarding the nature of the condition and the effects of the treatment with afamelanotide better reflect the patient experience. For example, it is now acknowledged that EPP is a disability with severe and untreatable	Thank you for your comments. The individual comments relating to the executive summary have been responded to below.

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			neuropathic pain without a treatment option but that treatment with afamelanotide brings the patients in the normal range for light exposure and Quality of Life. Further, the accepted associated utility values for patients under treatment are comparable to the utilities found in the general population. In our opinion, a treatment that is accepted to make such a difference to the patients' lives should be made available to them, as this would promote equality of opportunity by enabling a normal life, eliminate unlawful discrimination and fosterer good relations between people with particular protected characteristics and others. Even more so, as (1) the costs for afamelanotide are considerably lower than the costs for other highly specialized technologies recommended for funding, and (2) the ICER of 121.233 GBP is now very close to the threshold for cost-effectiveness. Given the developments in the appraisals as described above, we suggest to collect further data on the safety and the effectiveness of afamelanotide within a Managed Access Agreement (MAA). The IPPN offers their support for the data collection and further discussions on aspects like the economic model and etc. Further, some aspects regarding consistency and transparency concerning the interpretations of the nature of the condition, the technology, the clinical and cost effectiveness evaluation, and procedural aspects should be improved.	
20	Patient organisation	The International Porphyria Patient Network (IPPN)	**Has all of the relevant evidence been taken into account?** **Nature of the condition:** We suggest including the mutations in the genes for ALAS2 and CLPX as additional causes for protoporphyria (for further aspects and literature, see below). **The technology:** As stated in previous submissions, one/the main mode of action of afamelanotide are its strong anti-inflammatory properties. Evidence form peer-reviewed publications has been submitted and we suggest including this aspect in the description of the technology.	The FED has been updated so it is clear that mutations of genes involved in the haem production pathway other than ferrochelatase can also cause EPP (section 2.1). The description of the technology is based on

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				afamelanotide's summary of product characteristics
21	Patient organisation	The International Porphyria Patient Network (IPPN)	**Are the summaries of the clinical effectiveness reasonable interpretations of the evidence?** Effect of expressing the trial results as average "minutes per day in sunlight without pain": We in particular appreciate the more accurate description of the randomised controlled trial (RCT) outcomes of afamelanotide as averaged values, that is, minutes per day in sunlight without pain. However, the consistency of the description and interpretation within the ECD (Sep. 2022) needs to be improved. The committee accurately describes the primary endpoint "minutes per day in sunlight without pain" as an averaged value: *"The committee was aware that measuring the effects of afamelanotide through light exposure times was affected by averaging – that is, the light exposure times reported in the clinical trials were averaged both between people and over time."* ECD (Sep. 2022, p.12) Further, the committee accepts that these averaged outcomes need to be understood within the normal range for this measure: *"For CUV039, this equates to an average of 23.1 minutes per day in daylight for people having afamelanotide, compared with 13.6 minutes per day for people having placebo, between 10:00 and 18:00; for context, the committee understood that healthy indoor workers spend an average of 22 minutes outdoors between 10:00 and 15:00 on summer weekdays."* P. 19¶4.26 (ECD Sep. 2022*)* With the above statements, it is acknowledged that patients under treatment have sunlight exposure times comparable to the general population. Nevertheless, when describing the patient experience, this insight is not considered: *"Furthermore, in their testimonies, patients reported that afamelanotide resulted in much better outcomes than it had in the clinical trials. For*	

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			example, a patient expert at the meeting stated that afamelanotide had allowed him to increase the time he spent in light by hours rather than by minutes (as had been seen in the trials) and described this as life changing." P.19¶ 4.26 (ECD Sep. 2022, emphasis added by the authors) Please reformulate and remove *"in much better outcomes than it had in the clinical trials"* and *"rather than by minutes (as had been seen in the trials)"*, as the trial outcome refers to the averaged value (i.e., minutes per day), while the testimony of the patients refer to their experience on the maximum possible time in sunlight. The maximum time a patient with EPP can stay in sunlight without a phototoxic reaction has been quantified in the observational study by Barman-Aksözen et al. (2020). In this study, for the Swiss cohort, the maximum time of 10 minutes (median) in sunlight without pain in patients without treatment increased to 180 minutes under treatment The study is included in the ECD (Sep. 2022) and provides the context for testimonies like the above mentioned one. Treatment effects are "highly uncertain" The ECD still states that the treatment effects would be highly uncertain: *"But it is very difficult to measure the effects of the condition and treatment, and* *although afamelanotide is an effective treatment the size of the benefits it provides is* *highly uncertain."* ECD (Sep. 2022), p. 3 ¶ 1.2 In the light of the discussions at the appeal hearing and the new evidence that has been submitted by the stakeholders and its assessment (like mentioned above), we think that the interpretation of the treatment size as "highly uncertain" needs to be revised.	This statement has been updated to avoid misinterpretation in comparison between patient testimonies and trial outcomes (section 4.25). It should be noted that the committee concluded that afamelanotide is effective and provides important benefits for patients (section 4.31). Because of the difficulty associated with measuring the impact of treatment, the size of treatment benefits remains highly uncertain.
22	Patient organisation	The International Porphyria Patient Network (IPPN)	**Are the summaries of the cost effectiveness reasonable interpretations of the evidence?** We would like to thank the committee for taking some of the suggestions and data provided in March 2022 by the IPPN into consideration for their	

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			current estimation of the cost effectiveness of afamelanotide. Unfortunately, the information shared with the stakeholders and/or provided in the ECD (Sep. 2022, p.32-33) regarding the adjustments of the economic model is not sufficient to assess whether the summaries of clinical and cost effectiveness represent a reasonable interpretation of the evidence and/or are not completely reasonable. <u>Increasing the transparency</u>: Regrettably, the final utility values and QALY gains etc. are not provided in the ECD (Sep. 2022). However, this information can be estimated from the provided information on costs, Incremental Cost Effectiveness Ratios (ICERs), time horizons and discount rates. To increase the transparency, and to foster the discussion with people having a limited knowledge in health economics evaluations, we suggest publishing the final utility values and QALY gains etc. Please let us know reasons we might not be aware of on why it might be justified to not release this information to the public in a more accessible way. <u>Baseline utilities</u>: Several aspects concerning the baseline utilities should be clarified: - For the current calculation of the QALY gain, data from the study by Holme et al. (2006) mapped into the EQ-5D has been used as the baseline utilities (as suggested by the IPPN). However, two different algorithms (by Norlin 2012 and by Curry & Conway 2006) were used for the mapping by the Evidence Review Group which resulted in different utilities. We would like to ask the committee to provide more detailed information, for example which mapping results have been used for the current calculation. - Further, the study by Holme et al. (2006) reports different severity classes. Patients from the “no effect” and “small effect” groups might not want or need treatment or might need less than 4 doses. Therefore, we would like to ask the committee to share which data has been used in the current model.	NICE are unable to publish QALY gains in the ECD or FED because various model parameters are considered commercial in confidence by the company. The QALY gains are not published to prevent back-calculation of confidential data as declared by the company. The Currie and Conway (2006) algorithm was used for the preferred model because it had been validated in an independent dataset. The utilities were very similar for the two algorithms (0.60) (section 4.51). The utility value for the total population was used (including the 12% of the Holme et al. (2006) cohort in the ‘no effect’ and ‘small’ categories). This is in line with the marketing authorisation.

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			- As stated in the ECD (Sep. 2022) the utility values from the IPPN Swiss EQ-5D feasibility study for people under long-term treatment with afamelanotide were adjusted to match that of the age-matched UK general population. For transparency reasons, the committee should state the utility values finally used. - How has the committee taken into account the adaptation of the patients to their condition? The committee needs to keep in mind that the patients included in the study by Holme et al. (2006) were individuals who never had access to an effective treatment, and therefore most likely were highly adapted to their EPP and had an ingrained light avoidance behaviour. Therefore, the reported QoL results likely underestimate the true burden of EPP, as discussed at the committee meetings. In contrast, patients who have been on long-term treatment and then were confronted with a treatment interruption represent the better estimate for untreated QoL values: This cohort already has overcome their behavioural adaptation and ingrained light avoidance, and their utility values are comparable to hypothetical individuals of the general population who would acquire EPP and suddenly experience its symptoms. - As discussed earlier, another potential source for utilities are proxy conditions. The IPPN pointed out that utilities from patients with acute burn injuries and utilities from patients suffering from neuropathic pain could be used for the modelling, as they resemble the symptoms of EPP. <u>Treatment interruption</u>: - The adjustment of the results for patients during the treatment interruption phase are unclear: *"Using the IPPN's EQ-5D patient survey results to inform the utility value for people with EPP on afamelanotide and the utility estimated from a treatment interruption for people having standard care: the committee preferred to adjust the utility value to match the utility value for the UK general population for a person the assumed starting age in the company's model."* ECD (Sep. 2022, p.33)	The final utility values are not published to prevent back-calculation of confidential data as declared by the company. There is currently a lack of suitable data on which analysis include assumptions about QALY impact of 'unlearning of light avoidance behaviour' could be based. A long-term observational study reported by Biolcati et al. (2015) did not show a clear trend in mean EPP-QoL scores over 5-6 years of treatment. It should also be noted that scenarios were run using values other than Holme et al. (2006). For example, a scenario was conducted using utility value for a treatment interruption from the feasibility study (0.331) and this value is similar to utility values seen in people with acute burn injuries and chronic neuropathic pain.

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			How can the utility value of a person in the treatment interruption phase be adjusted to a utility value of the UK general population? The UK general population does not have utility values for people with untreated EPP. Time horizon: - To make the evaluation of afamelanotide more consistent with that of other conditions, the IPPN suggested using a time horizon of 70 years. However, the committee for their model assumed a 60-year time horizon, but did not provided an explanation for their decision (ECD Sep. 2022, p. 33). Most time horizons assumed for conditions, which start in the childhood and have a near normal life expectancy with technologies recommended for funding by the HST committee are between 80 to more than 100 (!) years, with a maximum of 125 [sic!] years in the case of HST1. - In case the diagnostic delay was assumed to justify a shorter time horizon: In our experience from countries in which afamelanotide is available, the time to diagnosis decreases considerably with most patients are identified already during their childhood. The delay in time to diagnosis as given in the ECD is 22 years, with an age of onset shortly after birth (ECD Sep. 2022 p.8¶ 4.6). Further shortening the diagnostic delay will result in the patients having their diagnosis when becoming eligible for treatment at age 18. - While the time horizon does not influence the ICER, it in our understanding still affects the total QALY gain and therefore the potential for weighing which can make a difference for the decision making. According to the Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, (p 12), weighing applies to QALY gains above 10. From the information provided in the ECD (Sep 2022) on the plausible ICER, costs and the time horizon, and an assumed 3.5% discounting rate, we estimate that afamelanotide treatment with a the time horizon of	Utility values in both arms adjusted in line with decline in general population utility over time (section 4.51). The ERG noted that a 70-year time horizon would increase the ICER and would not reduce the uncertainty in the cost-effectiveness analysis. It explained that the increase in ICER is because the utility declines with age due to the age-adjustment of utility values, but the cost is constant each year. As per the NICE process and methods guide, if baseline utility values are extrapolated over long time horizons, they should be adjusted to reflect decreases in HRQoL seen in the general population and to make sure that they do not exceed general population values at a given age (section 4.44). For a QALY weighting to be applied (regardless of model starting age), compelling evidence would be required that treatment offers substantial QALY gains. The committee noted that health-related quality-of-life (HRQoL) evidence that was used to underpin the updated analyses was subject to considerable uncertainty. The committee concluded that there was not enough compelling evidence underpinning the analysis using the additional data submitted by the IPPN at the second consultation to apply a QALY weight (section 4.45). It should also be noted that because of limited data in treatment for older people, afamelanotide use is not advised in people over 70 (section 4.44).

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			70 years using the same model assumption would increase the discounted QALY gain to more than 10 QALYs. <u>Model parameters:</u> Open questions regarding the modelling concern: - Does the model account for the fact that the unlearning of the light avoidance behaviour is only necessary during the first few weeks to months? After the initial unlearning phase, for example, from year 3 onwards, the full benefit is experience from the beginning of the treatment phase. - How does the model deal with the patients who might not want or need 4 doses of afamelanotide per year? *"Both analyses included and assuming a dosage of 4 implants per year of afamelanotide to reflect clinical expert opinion (see section 4.42), a gradual onset of effect over 2 months, and a 4-month attenuation of the relative treatment effect after the fourth implant".* ECD (Sep. 2022, p. 33) - Assumed seasonality: "*However, on balance, it concluded that the ERG's analyses assuming that the effect of afamelanotide would build up over the first 2 months (as modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions*." (ECD Sep. 2022 p. 28-29) The model used to calculate the QALY gain assumes that the treatment effect decreases after the last implant. However, the model is based on the assumption of seasonality that is that the patients only need treatment during the sunny season. Therefore, either the utilities should not decrease (as the burden of disease should be less severe), or the patient should get treatment (because he/she suffers from EPP symptoms even in the less sunny months). How were these effects incorporated in the model assumptions? In case seasonality is assumed, a loss in treatment effect does not necessarily result in lower utilities.	There is currently a lack of suitable data on which analysis which include assumptions about QALY impact of 'unlearning of light avoidance behaviour' could be based. A long-term observational study reported by Biolcati et al. (2015) did not show a clear trend in mean EPP-QoL scores over 5-6 years of treatment. Assumption of 4 implants per year based on clinical expert opinion and data from Wensink et al. (2020) study. Scenarios with less than 4 implants per year have also previously been considered (section 4.46). Seasonality in the effects of EPP on utility is not explicitly modelled. The model estimates QALY gain from treatment averaged over the year. Thus, a flat baseline utility reflects mean utility through the year for the standard care arm with a comparative utility gain for the afamelanotide arm.

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			Data collection during the MAA: - Please indicate a time frame until the EQ-5D (or similar) data should be submitted. - The IPPN questions the scientific rationale for the proposed Vignette study, given that the collection of better-quality evidence is apparently possible, as shown by the feasibility study conducted in Switzerland and accepted for the economic model. According to the DSU document issued in 2020 on the collection of EQ-5D data, QoL results collected directly from the patients are preferable over indirect measurements like in the case of vignette studies. (Rowen et al. 2020) We would like the committee to elaborate on why in their assessment a vignette study is preferred over other/better forms of evidence in the case of EPP. Minor mistakes: - ECD (Sep. 2022) p. 15¶ 4.20: “EQ--D data”, should read: “EQ-5D data”. - ECD (Sep. 2022) p. 16¶4.21: “They completed the EQ-5dD-3L […]”. Please correct “EQ-5D-5L”. - On p. 17¶ 4.22 (ECD Sep. 2022), it is stated: *“The IPPN considered that this new evidence addressed the uncertainty in the analysis about quantifying the quality-adjusted life year (QALY) gain associated with afamelanotide.”* While the IPPN assesses that the suggested approach better reflects the QALY gain provided by the afamelanotide treatment, we also stated, "we are aware that the feasibility study and survey are limited, amongst other aspects, by the small sample size. However, the HST committee previously accepted QALY outcomes based on patient surveys, and vignette studies conducted with five to six participants only.” Committee papers (issued Sep. 2022), p. 73. We therefore suggest reformulating the sentence as follows:	The committee acknowledged that such approaches are not necessarily as robust as the preferred approaches specified in the NICE reference case, but that it would be reasonable to consider given the challenges associated with this condition (section 4.49). The committee also considered other approaches that could be used to quantify health benefits. While the vignette study remained the committee’s preferred method for the quantification of QALYs, it accepted that alternative approaches like those proposed by the company in the managed access agreement proposal could also generate utility values (section 4.56). These minor errors have now been corrected in the FED.

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			*"The IPPN considered that this new evidence **better** addressed the uncertainty in the analysis about quantifying the quality-adjusted life year (QALY) gain associated with afamelanotide **and is comparable to methods previously accepted**."* Outlook: The IPPN renews its offer to work together with experts from NICE and/or the evidence review group to improve the model and to share data regarding the EQ-5D and other studies.	This sentence has been updated as suggested.
23	Patient organisation	The International Porphyria Patient Network (IPPN)	**Procedural aspects:** While in general the documentation and access to information on the appraisal processes at NICE is well organised and reasonably structured, we would like to point out that inaccurate information remains in the related documents and on the website. Further, some relevant information and documents have not been made public. Some of the issues have been discussed for example during the stakeholder workshop and the fourth committee meeting held 6 July 2022 and a comprehensive list can be provided upon request. Examples are: - The entire documentation of the third committee meeting held 14 March 2019, including the related submissions of new evidence and the ECD document issued in February 2020 are still missing from the website (last accessed 20 Oct. 2022). - Confusing ambiguities in the documents: For example, the ECD issued in Feb. 2020 and shared with the stakeholders was named ECD2. However, the current ECD issued in Sep 2022 is also named ECD2. (We for clarification in this submission referred to the documents as "ECD (Feb. 2020)" and "ECD (Sep. 2022)"). - Relevant information should be accessible: To fully assess whether the evidence has been taken into account and the ECD provides a reasonable interpretation of the evidence, the stakeholders and the public would need access to all the relevant information. However, the ECD (Sep. 2022) for example does not report the final QALY gain or how the	The NICE website has been updated to include appropriate ECD numbers and dates.

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			economic model has been adjusted in detail (see comments regarding cost-effectiveness, above). - Changes in the narrative of the procedure: (1) On slide 7 of the presentation (issued Sep 2022) of the committee meeting held 6 July 2022, it is stated under ECM3 Mar 2019: “Appraisal paused to give stakeholders an opportunity to explore further ways to obtain evidence”. This information is incorrect: The reason given to the stakeholders (and stated on the website under the “timeline” section) to pause the appraisal in May 2020 is the COVID-19 pandemic. In June 2020, the restart of the appraisal was announced, but no further information on the timeline was provided at that time. Formal activities were only resumed in December 2021, when the stakeholders were invited to a workshop was organised by NICE. Without clear information on the timeline, it is not possible, for example, to plan and conduct bigger studies to generate evidence. . - The new evidence submitted by the stakeholders in March 2022 was assessed by the evidence review group (ERG) Southampton Health Technology Assessments Centre (SHTAC). Regrettably, the stakeholders were neither informed nor involved in the assessment and had not possibility to provide feedback and information and/or clarify open questions before the committee meeting held on 6 July 2022, although they offered to provide their assistance. The stakeholders for example would have noticed that the entire submission of new evidence from the British Association of Dermatologists has not been forwarded to the ERG, a mistake that only became apparent one day before the committee meeting held 6 July 2022. Given the delay of the appraisal of already more than three years because of the pandemic (while other appraisals continued…). we think that NICE should do everything in their power to at least now enable a timely process. As patients with EPP living in England have no treatment option, every unnecessary delay and inefficiency is ethically questionable.	The slide was updated at the recent committee meeting to make clear that further to the appraisal being paused to give stakeholders an opportunity to explore further ways to obtain evidence, there were also delays due to the COVID-19 pandemic. Stakeholders were given the opportunity to provide feedback during the committee meeting and during the subsequent appraisal consultation.
24	Patient organisation	The International Porphyria	**NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please**	

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		Patient Network (IPPN)	**let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:** **• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;** **• could have any adverse impact on people with a particular disability or disabilities.** **Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.** <u>Nature of the condition - mutations in ALAS2 and CLPX cause protoporphyria, too:</u> The IPPN would like to make the committee aware that with the current description, a small subgroup of patients could be excluded from the treatment. By stating that: "*Erythropoietic protoporphyria (EPP) is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase."* (ECD September 2022, p. 4) other causes for the disease are not considered in the description of the condition. Protoporphyria can also be the result of gain-of-functions mutations in the genes for delta-aminolevulinate synthase 2 (ALAS2, the first enzyme of the heme biosynthetic pathway) and caseinolytic mitochondrial matrix peptidase chaperone subunit (CLPX, a chaperone of ALAS2). Both genetic defects cause a similar clinical presentation regarding the phototoxicity as loss-of-function mutations in the gene for ferrochelatase. In case these patients with protoporphyria are not mentioned in the ECD, there is a risk that they might become excluded from the treatment and unlawfully discriminated in case afamelanotide is made available by the NHS. References:	The FED has been updated so it is clear that mutations of genes involved in the haem production pathway other than ferrochelatase can also cause EPP (section 2.1).

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			Whatley, S. D., Ducamp, S., Gouya, L., Grandchamp, B., Beaumont, C., Badminton, M. N., ... & Puy, H. (2008). C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. The American Journal of Human Genetics, 83(3), 408-414. Yien, Y. Y., Ducamp, S., van der Vorm, L. N., Kardon, J. R., Manceau, H., Kannengiesser, C., ... & Paw, B. H. (2017). Mutation in human CLPX elevates levels of δ-aminolevulinate synthase and protoporphyrin IX to promote erythropoietic protoporphyria. Proceedings of the National Academy of Sciences, 114(38), E8045-E8052. <u>Access to afamelanotide is an ethical imperative:</u> *"The committee recognised that phototoxic reactions cause serious and severe symptoms,* *including intense pain and extreme tiredness, that last for days."* (ECD Sep. 2022, p. 6) The committee in the ECD (Sep 2022) acknowledged that treatment with afamelanotide brings the patients in the normal range for light exposure which is only possible if under treatment the symptoms as described above are no longer present. The committee further accepted that the Quality of Life normalised under treatment and that the associated utility values for patients under treatment are comparable to the utilities found in the general population. **In our opinion, a treatment that is accepted to make such a difference to the patients' lives must be made available to them**, as this would promote equality of opportunity by enabling a normal life, eliminate unlawful discrimination and fosterer good relations between people with particular protected characteristics and others. Even more so, as (1) the costs for afamelanotide are considerably lower than the costs for other highly specialized technologies recommended for funding, and (2) the ICER of 121.233 GBP is now very close to the threshold for cost-effectiveness.	The committee considered the nature of EPP as a disability throughout and understood its duties under the Equality Act. This is documented throughout the FED (in particular, sections 4.8, 4.22, 4.45, 4.47, 4.49 and 4.59). The decision for funding is not based on the list price of technologies. The committee concluded that it was appropriate to consider the ICERs for afamelanotide as part of its consideration of value for money (section 4.42).

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25	Professional organisation	British Association of Dermatologists (the BAD)	**Has all of the relevant evidence been taken into account?** Thank you. The BAD is unaware of further relevant evidence to take into account other than that presented in the Evaluation Consultation Document September 2022.	Thank you for your comments. No action required
26	Professional organisation	British Association of Dermatologists (the BAD)	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** The BAD is appreciative of the further time and attention paid to the potential funding of this breakthrough drug in the treatment of the disabling disorder, EPP. The BAD notes a major change in the calculations made by NICE on the cost effectiveness of afamelanotide in EPP. NICE now finds that the ICER based on their original model, which ranged between £1.34m and £1.73m per QALY gained, were unlikely to be plausible. Taking into account evidence that has been supplied by the patient organisation IPPN has led NICE to revise the ICER estimate to between £121,233 and £231,320 per QALY gained. Specifically, NICE now considers that a plausible ICER is £121,233 per QALY gained as this scenario includes its preferred assumption, i.e. with reference to EQ-5D data. This is close to the £100,000 threshold per QALY required for funding. As there is acknowledgement by NICE that remaining uncertainties remain due to the challenges of sufficiently capturing the benefit of this treatment in EPP (described through many strands of evidence including strong patient testimony), and that the cost-effectiveness analyses for afamelanotide are very challenging (e.g. 1, page 3), the BAD respectfully asks NICE to now speedily fund afamelanotide for the treatment of EPP.	The committee considered a range of evidence and options within a managed access agreement that would allow reconsideration with a higher degree of certainty about QALY gains and the value of money for afamelanotide (section 4.56). However, it noted that that for a technology to be considered for a managed access agreement, it needs to be plausibly cost effective. 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 (section 4.57).
27	Professional organisation	British Association of Dermatologists (the BAD)	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** *"Afamelanotide has a marketing authorisation in the UK under exceptional circumstances"* (3, page 4). Can NICE kindly explain what they mean by this (presumably this relates to Scotland although this is not specified?)	As per afamelanotide's summary of product characteristics, this means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
28	Professional organisation	British Association of Dermatologists (the BAD)	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** EQ--D data should be corrected to EQ-5D data (4.20, page 15)	This has been updated in the FED.
29	Professional organisation	British Association of	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations**	

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		Dermatologists (the BAD)	**of the evidence?** The BAD clinical experts agree that the anti-oxidant effect of afamelanotide could only be speculated upon, thus in the sentence (4.4, page 28, third sentence from bottom of page), we would propose adjusting to: *"…the clinical experts describe how the protective effects of afamelanotide (melanisation and presumed anti-oxidant effect) need time to build up after the first implant and persist for a period of time after the last implant."*	This has been updated in the FED.
30	Professional organisation	British Association of Dermatologists (the BAD)	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** While the new evidence that was taken into account led to the above (2) revision of the ICER calculation, other new evidence was dismissed. Several new strands of evidence were provided including from a prospective, post-authorisation observational study, retrospective chart review and a longitudinal case-control study (4.30, page 21-22). Despite some limitations of the data, it was disappointing that NICE felt they could not take into account any of these data on the benefits of afamelanotide treatment in EPP, particularly in view of the acknowledged difficulties in capturing benefits in this disability (1, page 3 and 4.32, page 23). *"The committee noted that it was not possible to quantify the underestimation".* (4.38, page 27)	The committee acknowledged that the recently published evidence provided more information on the treatment effects of afamelanotide. However, it noted the limitations of the data outlined by the ERG, and was aware that none of the data provided could be used to inform the economic model. The committee concluded that it would take the study results into account in its decision making (FED section 4.30).
31	Professional organisation	British Association of Dermatologists (the BAD)	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** The BAD has provided information and responses to NICE on this topic in 2016, 2017, 2018, 2019 and 2022 and during several instances over these years has strongly supported the proposals for a managed access agreement (MAA), if NICE should not feel that there is adequate evidence for drug funding outright. The BAD regrets the years that have passed without access to this treatment by patients in England (despite its availability for many years in several other countries) and continues to strongly recommend this route if full funding cannot be recommended by NICE (point 2 above). As acknowledged by NICE, there is a wealth of evidence that the drug is effective in this complex disability, and moreover, the overall financial outlay is relatively low. Respectfully, we ask that NICE reach the logical solution to progress to an MAA based on	The committee considered a managed access agreement proposal and acknowledged the launch of the IMF (sections 4.54- 4.57).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			current evidence, without further delay. Such an MAA would, naturally, incorporate data on benefits of the treatment.	
32	Professional organisation	British Association of Dermatologists (the BAD)	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** NICE specified that the Innovative Medicines Fund (IMF) had launched since afamelanotide was last considered and that it requires the company to make a new proposal for commercial access in line with this. The content of this remains a private matter between NICE and the company and the BAD is therefore unable to comment on this, but trusts that incorporation of the IMF procedure would occur in a manner enabling a positive outcome.	The committee considered a managed access agreement proposal (sections 4.54- 4.57).
33	Professional organisation	British Association of Dermatologists (the BAD)	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The aspect of the specific disability of EPP continues to cause difficulty in the appraisal of the impact of EPP and its treatment, including considerable challenges in evidence collection. Therefore, there are still aspects that need particular consideration to ensure there is no discrimination of this patient group on the grounds of their disability.	The committee considered the nature of EPP as a disability throughout and understood its duties under the Equality Act. This is documented throughout the FED (in particular, sections 4.8, 4.22, 4.45, 4.47, 4.49 and 4.59).
34	Online response		I don't understand why a treatment that removes almost all symptoms of EPP is not recommended? As a XLEPP patient I would do anything to have this treatment. To the point me and my family have considered moving countries for me to gain access. That's how life changing it would be for me.	Thank you for your comment. The committee considered a range of evidence and options within a managed access agreement that would allow reconsideration with a higher degree of certainty about QALY gains and the value of money for afamelanotide (section 4.56). However, it noted that that for a technology to be considered for a managed access agreement, it needs to be plausibly cost effective. 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 (section 4.57).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
35	Online response		The potential benefits of this treatment are undeniably positive for me as an EPP sufferer. The thought of not having to be concerned by the weather forecast every day is so exciting as currently my life is dependant on what the weather is like. If the forecast is for a sunny day, any plans I had need to be cancelled and I spend the day sitting indoors. The affect this has on my mental health is huge and especially after a period of prolonged warm weather, I find myself becoming miserable and depressed. On the physical pain I feel on the occasions I do need to go outside on a hot day, they are unbearable and I can't do anything but sit in front of a fan in a cold dark room. The only way I can describe it is if you imagine your blood is boiling under your skin. There's no way to cool it down and all I can do is scratch at the burnt areas until its raw which actually makes it worse. I tell people to think of how it feels when you open the oven and the heat hits your face, it's like that but constantly all over your body. Although I was unable to join any of the trials, the stories I heard from people who did filled me with hope as I heard how this treatment literally changed their lives. The ability to live a 'normal life' is something that right now, myself and people with EPP can only dream of. The ability to go to the shop if we want to, see friends or family during the summer or just sit near a window are things that so many take for granted but for us, it's all we want to do and this treatment gives us the potential opportunity to do just that.	Thank you for your comment. The committee recognised that EPP is a serious, debilitating and disabling condition with far-reaching effects on the lives of patients and their families (section 4.4). The committee considered a range of evidence including clinical trial results and patient testimonies (section 4.25). The committee recognised that afamelanotide is effective and provides important benefits for patients (section 4.31).
36	Online response		It is not clear to me how this conclusion has been reached. I have talked to many EPP patients before and during Afamelanotide treatment and can attest to the fact that this is a life changer for them. They become functioning and productive, contributing, members of society under treatment. The patients I know personally were hardly able to handle any sunlight at all, and under sceness treatment have been able to tolerate the sun just as well as me, who doesn't have EPP. This effect is definitely measurable and has in the past been measured and published. So I ask you kindly to reconcider and adjust your recommendation.	Thank you for your comment. The committee considered a range of evidence including clinical trial results and patient testimonies (section 4.25). The committee recognised that afamelanotide is effective and provides important benefits for patients (section 4.31).
37	Online response		"I don't understand why a treatment that removes almost all symptoms of EPP is not recommended? As a EPP patient I would do anything to have this treatment, I would literally give an arm to feel normal, like other human beings. Why am I not allowed to feel normal, why would you not consider my overall health? My happiness? It would mean the world to me to be able to watch my children compete in their sporting events, to be able to walk my dog, to be able to drive to a shop, to be able to even hang my wash up? To avoid abuse I get in the streets for walking around, fully clothed, hiding under an umbrella in 30 degrees heat? To not swell up like and be in constant pain with sleepless nights simply because I	Thank you for your comment. The committee recognised that EPP is a serious, debilitating and disabling condition with far-reaching effects on the lives of patients and their families (section 4.4).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			got caught out? That's how life changing it would be for me. Also, as the annual treatment costs per person is not that high (48080 GBP with four implants per year, and 36030 with three), it is ethically questionable why the treatment is not made available. Treatments previously recommended by the same committee have list prices of 125000 to > 600000 GB? For me, and many other people we are struggling to understand why it is still not recommended? EPP affects my everyday life and the life of my family and friends. I have to constantly think about if I'm going to be in visible sun light. For example popping to the shop, sitting in the living room near windows, driving in the car, reflections from mirrors, walking in other peoples shadows. I struggling with depression and anxiety as I feel I am so different to everyone around me and they don't understand how I feel and they can live normally. I often feel that others think I'm being over the top, which is a horrible way to feel. If there is something that can make this happen, we should be allowed it."	The decision for funding is not based on the list price of technologies. The committee concluded that it was appropriate to consider the ICERs for afamelanotide as part of its consideration of value for money (section 4.42).
38	Online response		"I don't understand why a treatment that removes almost all symptoms of EPP is not? As a EPP patient I would do anything to have this treatment, I would literally give an arm to feel normal, like other human beings. Why am I not allowed to feel normal, why would you not consider my overall health? My happiness? It would mean the world to me to be able to watch my children compete in their sporting events, to be able to walk my dog, to be able to drive to a shop, to be able to even hang my wash up? To avoid abuse I get in the streets for walking around, fully clothed, hiding under an umbrella in 30 degrees heat? To not swell up like and be in constant pain with sleepless nights simply because I got caught out? That's how life changing it would be for me. Also, as the annual treatment costs per person is not that high (48080 GBP with four implants per year, and 36030 with three), it is ethically questionable why the treatment is not made available. Treatments previously recommended by the same committee have list prices of 125000 to > 600000 GB? For me, and many other people we are struggling to understand why it is still not recommended? EPP affects my everyday life and the life of my family and friends. I have to constantly think about if I'm going to be in visible sun light. For example popping to the shop, sitting in the living room near windows, driving in the car, reflections from mirrors, walking in other peoples shadows. I struggling with depression and anxiety as I feel I am so different to everyone around me and they don't understand how I feel and they can live normally. I often feel that others think I'm being over the top, which is a horrible way to feel. If there is something that can make this happen, we should be allowed it."	Thank you for your comment. The committee recognised that EPP is a serious, debilitating and disabling condition with far-reaching effects on the lives of patients and their families (section 4.4). The decision for funding is not based on the list price of technologies. The committee concluded that it was appropriate to consider the ICERs for afamelanotide as part of its consideration of value for money (section 4.42).

NICE National Institute for Health and Care Excellence

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	CLINUVEL (UK) LTD
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Section 1.2 *"There is some evidence from clinical trials that afamelanotide provides benefits for people with EPP".* Why does NICE choose to qualify this sentence with the use of the word "some"? This wording is not used in any other HST process to describe evidence from clinical trials. The statement is a definitive one – there either is, or is not, evidence from clinical trials of the benefit of afamelanotide to EPP patients. The Committee has previously been found by NICE's appeal panel that describing the effect of treatment as "small" is unreasonable. Deliberately chosen wording aims to shed doubts about efficacy, while prescribers and patients have used the drug without interruption for 8 years now under conditions of use, and 16 years including all clinical trials and compassionate use. 'People with EPP' is a lay term for patients lifelong affected by a disease poorly characterised.
2	Section 2.1 *"caused by sunlight and some types of artificial light… sunlight avoidance"* Evidence provided to the Committee from multiple sources during the various consultations on this evaluation is that it is specific wavelengths of light along the visible spectrum – the Soret band, peaking at 408nm – which causes phototoxicity in EPP. More accurate phrasing would be "caused by light sources, both sunlight and artificial light emitted specifically along the visible spectrum above 400 nm" and "sun and generally, light avoidance".
3	Section 3.2 A broader safety profile than that seen in clinical trials is now taken into account as part of the summary of product characteristics.
4	Section 3.3 *"Afamelanotide has not been launched in the UK, but the company has stated that the cost of an implant will be £12,020 (excluding VAT)."* SCENESSE® has been launched in the UK and is prescribed to patients in Scotland under a patient access scheme. The approved NHS list price of the medication is £13,209 (ex VAT). The Company has notified NICE of the UK launch and Scottish program on a number of occasions, including at the 8 February 2022 Workshop, at Committee meeting 4 on 6 July 2022, on a call with the CEO of NICE on 26 July 2022, and in correspondence on 16 March 2022 and 14 July 2022.
5	Section 4.8 *"…the specific challenge in measuring the effect of the condition and its treatment on quality of life… It heard that there was an important lack of robust scientific instruments to measure such effects."* The EMA's opinion on scientific instruments – as presented to the Committee by the Company over six years – relates not only to the impact on patient QoL, but also more broadly to the overall impact of the disease and the Company's ability to generate data on efficacy and clinical benefit as per the EMA's outcome. While QoL may be the focus of section 4.8, this broader effect and finding is relevant to the overall assessment made by NICE.
6	Section 4.18 *"The company stated that it had consulted with EPP experts to develop the EPP-QoL. However, it was unable to provide the committee with a response to whether it had used standard methods for developing and validating this tool."* This statement is factually incorrect and contradicts the later statement that a peer-review publication validating the EPP-QoL that was provided to the Committee.

Please return to: **NICE DOCS**

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	The ECD is not written in a manner which reflects the chronological interactions on the review of afamelanotide, so it is unclear why statements such as the above remain. If a chronological representation of the review would have been made, then the ECD would not have omitted salient points, including all matters relating to the appeal panel (which is not mentioned at all, despite the Committee being found, for example, to have breached the Equality Act, 2010), contradictions on the use of qualitative data (as outlined in correspondence to NICE on 16 March 2022 and 14 July 2022 and discussed below) and the unexplained delays in the review process between the third Committee Meeting in 14 March 2019 and the "Stakeholder workshop" of 8 February 2022. The ECD intentionally cherry picks its arguments while omitting significant parts of the Company's arguments, as found back in the minutes and outcome of the Appeal Panel, July 2018. Further, it is unclear why the first sentence – which references the Company's undisputed work with EPP experts to develop the EPP-QoL – should be followed by a contradictory "however", which suggests that all work and expertise around the EPP-QoL should be questioned. The persistence of this approach is unreasonable and misleads the reader.
7	Section 4.19 *"The committee noted that, in a large observational study, DLQI had been shown to be sensitive to the effect of EPP on people with the condition…* *The committee concluded that, although DLQI had notable limitations, it had been one of the tools incorporated in the clinical trials at the outset to measure QoL and the results were relevant to its consideration of clinical effectiveness."* There is an inconsistency in the acceptance of evidence by the Committee. It is assumed – although this is not stated – that the study referenced is Holme et al (2006), which uses the DLQI in a cohort of UK EPP patients. A more recent UK study – Jong et al (2009), which was also submitted to the Committee, involves most of the authors of the 2006 study and is co-authored by both of the clinical expert stakeholders – recognised the challenges of studying photodermatoses and EPP and adapted the DLQI to include a longer recall period, as "a short time base of 1 week may 'miss' the QoL impact" in a disorder with intermittent symptoms and as no photodermatoses-specific QoL has been published. Rutter et al (2019) – also submitted to the Committee and co-authored by one of the clinical expert stakeholders – discusses these challenges in further detail. The Company has made considerable submissions to the Committee outlining the inappropriate nature of the DLQI for capturing disease benefit in EPP. Most importantly, the EMA had, in its review, accepted that the DLQI is not an appropriate tool for measuring the impact of disease and therapy in EPP, nevertheless the Committee persists in its arguments. The medical community of experts is no longer using the DLQI in EPP or most severe photodermatoses.
8	Section 4.24 *"[the Committee] also highlighted that it considers qualitative evidence as part of its careful deliberation on all the factors that have contributed to its conclusion. For example, it contributes to the understanding of the nature of the condition, and to interpreting the clinical evidence. 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."* The Company welcomes the Committee's recognition that qualitative evidence has been, and should further be, taken into account in the context of this evaluation. However, in this context it is erroneous for the Committee to criticise qualitative evidence submitted by CLINUVEL, patient groups and other stakeholders without noting that the Committee's current position contradicts earlier advice provided to the Company in the February 2020 and February 2022 draft ECDs – as highlighted in correspondence to NICE on 16 March 2022, 14 July 2022 and during the fourth Committee meeting on 6 July 2022 – which stated:

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	"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" As outlined above, if the ECD is to follow a chronological review of afamelanotide, this salient point should be reinstated, along with the formal response by the Committee chair during Committee meeting 4. It is further unclear to the Company why the draft February 2020 and February 2022 ECDs were never finalised or published by NICE.
9	Section 4.30 *"The ERG said that there was substantial uncertainty over the results. They have wide confidence intervals and there are limitations in reporting."* The Company notes that Wensink et al (2020) is the largest single cohort study of EPP ever published. It is unclear why the ERG's approach to this article – which is peer reviewed and published in *JAMA Dermatology* – is not more closely reviewed by the Committee as to whether it is a reasonable interpretation. Rather, the ERG's comments appear to be taken at face value and without critique. It is important to state that the Company is not involved in the publication of results as submitted by expert clinicians, and that editorial input is not provided.
10	Section 4.30 *"Barman-Aksözen et al. (2020)…..People having afamelanotide"* The terminology is odd and demonstrates lack of professionalism in dictum. We suggest "receiving treatment with afamelanotide" would be more appropriate.
11	Section 4.30 *"Wensink et al. (2021)……The ERG again noted a lack of clarity in the study over participant recall. It also pointed out that the instrument used to measure results had not been validated."* The Company agrees that this study, whilst interesting, has limited value in evaluating the impact of EPP on patients' quality of life and the effectiveness of treatment. The endpoint "time to prodrome" measures a subjective exposure time until patients experience a "warning" signal, but there is no data to support its use in evaluating disease impact or clinical benefit. While prodromes are a unique feature of EPP, their relationship to the length and severity of phototoxicity in EPP is not defined and to suggest a direct relationship between the onset of the prodromal phase and symptoms ignores the unique nature of the disease.
12	Section 4.30 *"The ERG said Minder et al. study results may have suggested positive results in relation to liver damage. But it added that, in clinical practice, tests other than those used in the study are likely to be used to assess liver damage."* The ERG's conclusions are factually incorrect and indicate a complete lack of understanding of clinical care and monitoring in EPP. PPIX and AST are primary biochemical markers of liver function in EPP patients and are used in routine UK and EU clinical practice to monitor for potential liver damage. Both of these markers are reported in the Minder et al. study, along with 13 other laboratory measures. Considerable evidence of the use of AST and PPIX levels to monitor liver function has been included in Minder et al., as well as publications submitted throughout the evaluation of afamelanotide. Based on the evidence submitted, it is unreasonable for the Committee to include such commentary from the ERG without adequate assessment and critique.
13	Section 4.40 *"The committee noted that the modelling was based on EPP-QoL data collected at 4 months, but that this data was also collected at 6 months, although from a smaller proportion of the trial population.*

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	This data had not been presented by the company. The committee considered that, if the EPP-QoL data was to be used, the longer follow-up data could have been useful to see. This was particularly because 1 clinical expert explained that the benefits of afamelanotide may take time to become apparent if people adapt their conditioned behaviour gradually" The Company notes that considerable QoL data from the use of the EPP-QoL has been made available to the Committee over the course of **the six year** review by the Committee, including long-term use in the Wensink et al (2020) and Minder et al (2021) studies, as well as the validation study (Biolcati et al, 2021). As a result, such a comment is not only unreasonable, in light of the evidence presented, but now also factually incorrect. As highlighted above, the Committee's omission to present a chronology breakdown of the review of afamelanotide leads to an ECD lacking detail and context.
14	Section 4.48 *"Before the second consultation the committee explored ways to quantify the health benefits described by patients' and clinical experts' testimonies in terms of QALYs. It suggested that utility scores for the economic model could be estimated through an indirect method such as a 'vignette' study."* Section 4.49 *"After the second consultation, the committee was disappointed that the company had chosen not to do a vignette study."* The Company has responded extensively to the Committee's requirement for a vignette study, as the only method by which new data can be evaluated for the review of afamelanotide and has explained in detail why we consider the Committee's position to be unreasonable and unfeasible. The publication of the ECD in the absence of the Company's response is unbalanced and we ask NICE to publish this correspondence as a matter of transparency. We note that vignettes feature heavily in the ECD, despite no evidence from the Committee that this methodology is suitable for use in EPP (it has not, for example, been validated for the disease, a major critique of the Committee and ERG of other tools presented to the Committee). The Company's position, as provided to NICE by letter dated 14 July 2022, is as follows: 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

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	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. Importantly, the Company's concerns and the issues raised in our letter of 14 July 2022 have not been answered of explained by NICE or the Committee either in correspondence, discussion or in the ECD.
15	Section 4.51 *"It recalled that it decided not to apply a QALY weighting (see section 4.44, and noted that the plausible ICER was above what could be acceptable for a highly specialised technology."* There is a typographical error in this sentence.
16	Section 4.53 *"The committee would welcome a new proposal for managed access from the company, including a data collection proposal and commercial access proposal, to explore whether a managed access agreement for afamelanotide would be feasible."* **Managed access agreement proposals submitted** The Company submitted a proposal for a managed access agreement prior to receipt of the ECD draft, as well as submitting a proposed managed access agreement in 2018, and requesting to submit or discuss managed access agreements in correspondence on 8 March 2019, 20 January 2020 and 14 July 2022, and at meetings on 11 June 2021, 8 February 2022 and 26 July 2022.

NICE National Institute for Health and Care Excellence

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

The Company most recently discussed a possible managed access agreement with NICE on 19 August 2022. At this time, NICE suggested that a draft ECD would be received within 2-3 weeks, with which the Company could refine a managed access agreement proposal. After receiving no correspondence for more than one month, the Company submitted a proposal for a managed access agreement on 21 September 2022. Access to the draft ECD was only granted by NICE on 27 September 2022.

Despite its best efforts to engage on a data collection agreement, the Company takes this opportunity to provide further context to the proposed managed access agreement and data collection proposal it has outlined.

Direct, quantitative approach to data collection
The Company considers that only a direct quantitative approach, based on validated, disease-specific tools, and which incorporates analyses of long-term data captured in England and similar countries is appropriate for a data collection under a proposed managed access agreement. This will allow for a more informed decision to be made about patient access and long-term NHS funding, as well as the viability of supplying SCENESSE® to the UK post-Brexit. Such an approach also best aligns with NICE's preferred methods for technology appraisal/evaluation for a patient population in which no further randomised controlled trials can ethically be conducted, and minimises the overall burden on patients and NHS staff asked to collect data.

CLINUVEL proposes a Data Collection Agreement which:

- Recognises that standard HRQoL methods are inappropriate for EPP, in part due to reasons consistent with findings of the European Medicines Agency (as set out in the European Public Assessment Report)
- Uses disease specific tools already in clinical use across Europe, with efforts focused on validating and mapping these to accepted HRQoL tools and measures.
- Accepts data from the ongoing post authorisation safety studies, real world evidence generated since 2016, consistent with the approach agreed during Committee Meeting 4 on 7 July 2022
- Incorporates disease specific tools developed to capture impact on patient QoL as well as overall disability (Inventory of Daily Activities).

Disease-specific tools
The Committee has repeatedly expressed concerns in relation to "uncertainties" around measures used in evaluation of EPP and afamelanotide, with a particular focus on the EPP Quality of Life (EPP-QoL) tool. For example, 4.18 of the ECD notes "The committee was also aware that the EPP-QoL had not been assigned preference weights and had not been mapped to an outcome measure that could provide preference weights. This meant that the measure could not be used to generate utility values". In order to address this, rather than seek to pursue methodologies which have no proven validity in EPP patients, the Company intends to work with existing tools for which extensive data are available.

There is an extensive body of data from the use of the EPP-QoL, with the tool first deployed in clinical trials and subsequently used over [redacted] times with patients post-authorisation. A partial validation of the tool has been completed (Biolcati et al., 2021).

In parallel, alongside EPP experts, CLINUVEL has developed an EPP-specific Inventory of Daily Activities (IDA) tool, which has been in use post-authorisation since 2016. The IDA seeks to capture information on the overall disability and restrictions placed on EPP patients, and changes to these over time.

CLINUVEL proposes to further the use of the EPP-QoL – as submitted annually to the EMA and FDA - and IDA to exhaustively determine whether these can be mapped to HRQOL measures and tools.

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	The proposed five year window for data collection and analysis is expected to provide time to capture sufficient English data (along with that already captured in Europe and Scotland) and implement the most appropriate approach. Up to twenty percent of EPP patients experience liver injury, with four percent suffering terminal liver failure requiring a life-saving transplantation. Recently published data (Minder et al., 2021) suggests that long-term treatment with SCENESSE® may have a hepatoprotective effect in EPP patients. CLINUVEL is investigating this new finding to determine whether similar outcomes are seen in the broader EPP patient cohort. If confirmed, the Company would seek to incorporate such an outcome in its data collection and evidence base. **Method of data capture – real world evidence** CLINUVEL has established the largest EPP disease registry, the European EPP Disease Registry or EEDR, data from which have already been accepted by NICE as part of the second consultation process. The Company proposes to extend the use of the EEDR into England to capture data on real world use of SCENESSE®, including the number of implants received per patient per annum, and deploying the EPP-QoL and IDA tools. Further measures on patient safety and treatment compliance – as previously provided to NICE – are also captured in the EEDR. The Company completes annual analyses of EEDR data, copies of which are provided to regulatory authorities (EMA, MHRA, FDA). **Commercial proposal** CLINUVEL has been advised by NHS England (9 November) that it has been unable to schedule a discussion on a commercial proposal between the Company, NHSE and NICE until 15 December 2022, after the closing of the consultation period; this had not previously been communicated to the Company. Consistent with the Company's transparent approach to pricing and uniform pricing policy (and the Scottish PAS), CLINUVEL would make SCENESSE® available at the uniform price to NHS England, recognising that it is more than six years since this price was first offered to the NHS and that no English EPP patients have received treatment coverage to date. The Company has already stated that it will commit to the principles of the Innovative Medicines Fund, should this be the pathway pursued by NHS England for SCENESSE®. **Timelines** Based on a proposed HST meeting in January 2023, CLINUVEL would be able to implement the proposed data collection plan in time for Spring 2023 in England, pending agreements with the few English centres willing and able to treat EPP patients.
17	**References** Biolcati, G., Hanneken, S., Minder, E. I., Neumann, N. J., Wilson, J. H. P., Wolgen, P. J., Wright, D. J., & Lloyd, A. J. (2021). Validation of a novel patient reported tool to assess the impact of treatment in erythropoietic protoporphyria: The EPP-QoL. Journal of Patient-Reported Outcomes, 5(1), 65. https://doi.org/10.1186/s41687-021-00345-7 Holme, S. A., Anstey, A. V., Finlay, A. Y., Elder, G. H., & Badminton, M. N. (2006). Erythropoietic protoporphyria in the U.K.: Clinical features and effect on quality of life. British Journal of Dermatology, 155(3), 574–581. https://doi.org/10.1111/j.1365-2133.2006.07472.x Jong, C. T., Finlay, A. Y., Pearse, A. D., Kerr, A. C., Ferguson, J., Benton, E. C., Hawk, J. L. M., Sarkany, R. P., McMullen, E., Rhodes, L. E., Farr, P. M., & Anstey, A. V. (2008). The quality of life of 790 patients with photodermatoses. The British Journal of Dermatology, 159(1), 192–197. https://doi.org/10.1111/j.1365-2133.2008.08581.x Minder, A.-E., Barman-Aksoezen, J., Schmid, M., Minder, E. I., Zulewski, H., Minder, C. E., & Schneider-Yin, X. (2021). Beyond pigmentation: Signs of liver protection during afamelanotide treatment in Swiss patients with erythropoietic protoporphyria, an observational study. Therapeutic

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Advances in Rare Disease, 2, 263300402110654. https://doi.org/10.1177/26330040211065453 Rutter, K. J., Ashraf, I., Cordingley, L., & Rhodes, L. E. (2019). Quality of life and psychological impact in the photodermatoses: A systematic review. The British Journal of Dermatology. https://doi.org/10.1111/bjd.18326

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Porphyria Association**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Not applicable**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are pleased that the additional evidence has been taken into account in the ECD 3, and pleased that the ICER is dramatically closer to the ICER threshold than it was in ECD 1 or 2. As a patient group, however, we are disappointed that a positive recommendation for routine use wasn't possible, though we are hopeful that the company, NHS England and NICE may be able to come to some arrangement to provide the medication under a Managed Access Agreement via the Innovative Medicines Fund. The body of evidence that Afamelanotide is a highly effective treatment for patients who do have access to it continues to grow. We therefore urge the company and NICE to find a way of working together more effectively, in order to close the remaining gap and get this medication to patients.
2	
3	
4	

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

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Please return to: **NICE DOCS**

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**International Porphyria Patient Network (IPPN)**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[No conflict of interest to declare]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Execute summary:** The IPPN appreciates that much of the submitted evidence has now been taken into account and that the understanding of the committee regarding the nature of the condition and the effects of the treatment with afamelanotide better reflect the patient experience. For example, it is now acknowledged that EPP is a disability with severe and untreatable neuropathic pain without a treatment option but that treatment with afamelanotide brings the patients in the normal range for light exposure and Quality of Life. Further, the accepted associated utility values for patients under treatment are comparable to the utilities found in the general population. In our opinion, a treatment that is accepted to make such a difference to the patients' lives should be made available to them, as this would promote equality of opportunity by enabling a normal life, eliminate unlawful discrimination and fosterer good relations between people with particular protected characteristics and others. Even more so, as (1) the costs for afamelanotide are considerably lower than the costs for other highly specialized technologies recommended for funding, and (2) the ICER of 121.233 GBP is now very close to the threshold for cost-effectiveness. Given the developments in the appraisals as described above, we suggest to collect further data on the safety and the effectiveness of afamelanotide within a Managed Access Agreement (MAA). The IPPN offers their support for the data collection and further discussions on aspects like the economic model and etc. Further, some aspects regarding consistency and transparency concerning the interpretations of the nature of the condition, the technology, the clinical and cost effectiveness evaluation, and procedural aspects should be improved.
2	**Has all of the relevant evidence been taken into account?** **Nature of the condition:** We suggest including the mutations in the genes for ALAS2 and CLPX as additional causes for protoporphyria (for further aspects and literature, see below). **The technology:** As stated in previous submissions, one/the main mode of action of afamelanotide are its strong anti-inflammatory properties. Evidence form peer-reviewed publications has been submitted and we suggest including this aspect in the description of the technology.
3	**Are the summaries of the clinical effectiveness reasonable interpretations of the evidence?** <u>Effect of expressing the trial results as average "minutes per day in sunlight without pain"</u>: We in particular appreciate the more accurate description of the randomised controlled trial (RCT) outcomes of afamelanotide as averaged values, that is, minutes per day in sunlight without pain. However, the consistency of the description and interpretation within the ECD (Sep. 2022) needs to be improved. The committee accurately describes the primary endpoint "minutes per day in sunlight without pain" as an averaged value: *"The committee was aware that measuring the effects of afamelanotide through light exposure times was affected by averaging – that is, the light exposure times reported in the clinical trials were averaged both between people and over time."* ECD (Sep. 2022, p.12)

Please return to: **NICE DOCS**

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	Further, the committee accepts that these averaged outcomes need to be understood within the normal range for this measure: *"For CUV039, this equates to an average of 23.1 minutes per day in daylight for people having afamelanotide, compared with 13.6 minutes per day for people having placebo, between 10:00 and 18:00; for context, the committee understood that healthy indoor workers spend an average of 22 minutes outdoors between 10:00 and 15:00 on summer weekdays."* P. 19¶4.26 (ECD Sep. 2022*)* With the above statements, it is acknowledged that patients under treatment have sunlight exposure times comparable to the general population. Nevertheless, when describing the patient experience, this insight is not considered: *"Furthermore, in their testimonies, patients reported that afamelanotide resulted in much better outcomes than it had in the clinical trials. For example, a patient expert at the meeting stated that afamelanotide had allowed him to increase the time he spent in light by hours rather than by minutes (as had been seen in the trials) and described this as life changing."* P.19¶ 4.26 (ECD Sep. 2022, emphasis added by the authors) Please reformulate and remove *"in much better outcomes than it had in the clinical trials"* and *"rather than by minutes (as had been seen in the trials)"*, as the trial outcome refers to the averaged value (i.e., minutes per day), while the testimony of the patients refer to their experience on the maximum possible time in sunlight. The maximum time a patient with EPP can stay in sunlight without a phototoxic reaction has been quantified in the observational study by Barman-Aksözen et al. (2020). In this study, for the Swiss cohort, the maximum time of 10 minutes (median) in sunlight without pain in patients without treatment increased to 180 minutes under treatment The study is included in the ECD (Sep. 2022) and provides the context for testimonies like the above mentioned one. Treatment effects are "highly uncertain" The ECD still states that the treatment effects would be highly uncertain: *"But it is very difficult to measure the effects of the condition and treatment, and although afamelanotide is an effective treatment the size of the benefits it provides is highly uncertain."* ECD (Sep. 2022), p. 3 ¶ 1.2 In the light of the discussions at the appeal hearing and the new evidence that has been submitted by the stakeholders and its assessment (like mentioned above), we think that the interpretation of the treatment size as "highly uncertain" needs to be revised.
4	**Are the summaries of the cost effectiveness reasonable interpretations of the evidence?** We would like to thank the committee for taking some of the suggestions and data provided in March 2022 by the IPPN into consideration for their current estimation of the cost effectiveness of afamelanotide. Unfortunately, the information shared with the stakeholders and/or provided in the ECD (Sep. 2022, p.32-33) regarding the adjustments of the economic model is not sufficient to assess whether the summaries of clinical and cost effectiveness represent a reasonable interpretation of the evidence and/or are not completely reasonable. Increasing the transparency: Regrettably, the final utility values and QALY gains etc. are not provided in the ECD (Sep. 2022). However, this information can be estimated from the provided information on costs, Incremental Cost Effectiveness Ratios (ICERs), time horizons and discount rates. To increase the transparency, and to foster the discussion with people having a limited knowledge in health economics evaluations, we

suggest publishing the final utility values and QALY gains etc.
Please let us know reasons we might not be aware of on why it might be justified to not release this information to the public in a more accessible way.

Baseline utilities:

Several aspects concerning the baseline utilities should be clarified:

- For the current calculation of the QALY gain, data from the study by Holme et al. (2006) mapped into the EQ-5D has been used as the baseline utilities (as suggested by the IPPN). However, two different algorithms (by Norlin 2012 and by Curry & Conway 2006) were used for the mapping by the Evidence Review Group which resulted in different utilities. We would like to ask the committee to provide more detailed information, for example which mapping results have been used for the current calculation.

- Further, the study by Holme et al. (2006) reports different severity classes. Patients from the "no effect" and "small effect" groups might not want or need treatment or might need less than 4 doses. Therefore, we would like to ask the committee to share which data has been used in the current model.

- As stated in the ECD (Sep. 2022) the utility values from the IPPN Swiss EQ-5D feasibility study for people under long-term treatment with afamelanotide were adjusted to match that of the age-matched UK general population. For transparency reasons, the committee should state the utility values finally used.

- How has the committee taken into account the adaptation of the patients to their condition?
The committee needs to keep in mind that the patients included in the study by Holme et al. (2006) were individuals who never had access to an effective treatment, and therefore most likely were highly adapted to their EPP and had an ingrained light avoidance behaviour. Therefore, the reported QoL results likely underestimate the true burden of EPP, as discussed at the committee meetings. In contrast, patients who have been on long-term treatment and then were confronted with a treatment interruption represent the better estimate for untreated QoL values: This cohort already has overcome their behavioural adaptation and ingrained light avoidance, and their utility values are comparable to hypothetical individuals of the general population who would acquire EPP and suddenly experience its symptoms.

- As discussed earlier, another potential source for utilities are proxy conditions. The IPPN pointed out that utilities from patients with acute burn injuries and utilities from patients suffering from neuropathic pain could be used for the modelling, as they resemble the symptoms of EPP.

Treatment interruption:

- The adjustment of the results for patients during the treatment interruption phase are unclear:

"Using the IPPN's EQ-5D patient survey results to inform the utility value for people with EPP on afamelanotide and the utility estimated from a treatment interruption for people having standard care: the committee preferred to adjust the utility value to match the utility value for the UK general population for a person the assumed starting age in the company's model." ECD (Sep. 2022, p.33)

How can the utility value of a person in the treatment interruption phase be adjusted to a utility value of the UK general population? The UK general population does not have utility values for people with untreated EPP.

Time horizon:

- To make the evaluation of afamelanotide more consistent with that of other conditions, the IPPN

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	suggested using a time horizon of 70 years. However, the committee for their model assumed a 60-year time horizon, but did not provided an explanation for their decision (ECD Sep. 2022, p. 33). Most time horizons assumed for conditions, which start in the childhood and have a near normal life expectancy with technologies recommended for funding by the HST committee are between 80 to more than 100 (!) years, with a maximum of 125 [sic!] years in the case of HST1. - In case the diagnostic delay was assumed to justify a shorter time horizon: In our experience from countries in which afamelanotide is available, the time to diagnosis decreases considerably with most patients are identified already during their childhood. The delay in time to diagnosis as given in the ECD is 22 years, with an age of onset shortly after birth (ECD Sep. 2022 p.8¶ 4.6). Further shortening the diagnostic delay will result in the patients having their diagnosis when becoming eligible for treatment at age 18. - While the time horizon does not influence the ICER, it in our understanding still affects the total QALY gain and therefore the potential for weighing which can make a difference for the decision making. According to the Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, (p 12), weighing applies to QALY gains above 10. From the information provided in the ECD (Sep 2022) on the plausible ICER, costs and the time horizon, and an assumed 3.5% discounting rate, we estimate that afamelanotide treatment with a the time horizon of 70 years using the same model assumption would increase the discounted QALY gain to more than 10 QALYs. <u>Model parameters:</u> Open questions regarding the modelling concern: - Does the model account for the fact that the unlearning of the light avoidance behaviour is only necessary during the first few weeks to months? After the initial unlearning phase, for example, from year 3 onwards, the full benefit is experience from the beginning of the treatment phase. - How does the model deal with the patients who might not want or need 4 doses of afamelanotide per year? *“Both analyses included and assuming a dosage of 4 implants per year of afamelanotide to reflect clinical expert opinion (see section 4.42), a gradual onset of effect over 2 months, and a 4-month attenuation of the relative treatment effect after the fourth implant”.* ECD (Sep. 2022, p. 33) - Assumed seasonality: "*However, on balance, it concluded that the ERG’s analyses assuming that the effect of afamelanotide would build up over the first 2 months (as modelled in its base case), and that the treatment effect would slowly decrease over 6 months after the last implant, used plausible assumptions*." (ECD Sep. 2022 p. 28-29) The model used to calculate the QALY gain assumes that the treatment effect decreases after the last implant. However, the model is based on the assumption of seasonality that is that the patients only need treatment during the sunny season. Therefore, either the utilities should not decrease (as the burden of disease should be less severe), or the patient should get treatment (because he/she suffers from EPP symptoms even in the less sunny months). How were these effects incorporated in the model assumptions? In case seasonality is assumed, a loss in treatment effect does not necessarily result in lower utilities. <u>Data collection during the MAA:</u> - Please indicate a time frame until the EQ-5D (or similar) data should be submitted.

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	- The IPPN questions the scientific rationale for the proposed Vignette study, given that the collection of better-quality evidence is apparently possible, as shown by the feasibility study conducted in Switzerland and accepted for the economic model. According to the DSU document issued in 2020 on the collection of EQ-5D data, QoL results collected directly from the patients are preferable over indirect measurements like in the case of vignette studies. (Rowen et al. 2020) We would like the committee to elaborate on why in their assessment a vignette study is preferred over other/better forms of evidence in the case of EPP. Minor mistakes: - ECD (Sep. 2022) p. 15¶ 4.20: “EQ--D data”, should read: “EQ-5D data”. - ECD (Sep. 2022) p. 16¶4.21: “They completed the EQ-5dD-3L […]”. Please correct “EQ-5D-5L”. - On p. 17¶ 4.22 (ECD Sep. 2022), it is stated: *“The IPPN considered that this new evidence addressed the uncertainty in the analysis about quantifying the quality-adjusted life year (QALY) gain associated with afamelanotide.”* While the IPPN assesses that the suggested approach better reflects the QALY gain provided by the afamelanotide treatment, we also stated, "we are aware that the feasibility study and survey are limited, amongst other aspects, by the small sample size. However, the HST committee previously accepted QALY outcomes based on patient surveys, and vignette studies conducted with five to six participants only.” Committee papers (issued Sep. 2022), p. 73. We therefore suggest reformulating the sentence as follows: *“The IPPN considered that this new evidence **better** addressed the uncertainty in the analysis about quantifying the quality-adjusted life year (QALY) gain associated with afamelanotide **and is comparable to methods previously accepted**.”* Outlook: The IPPN renews its offer to work together with experts from NICE and/or the evidence review group to improve the model and to share data regarding the EQ-5D and other studies.
5	**Procedural aspects:** While in general the documentation and access to information on the appraisal processes at NICE is well organised and reasonably structured, we would like to point out that inaccurate information remains in the related documents and on the website. Further, some relevant information and documents have not been made public. Some of the issues have been discussed for example during the stakeholder workshop and the fourth committee meeting held 6 July 2022 and a comprehensive list can be provided upon request. Examples are: - The entire documentation of the third committee meeting held 14 March 2019, including the related submissions of new evidence and the ECD document issued in February 2020 are still missing from the website (last accessed 20 Oct. 2022). - Confusing ambiguities in the documents: For example, the ECD issued in Feb. 2020 and shared with the stakeholders was named ECD2. However, the current ECD issued in Sep 2022 is also named ECD2. (We for clarification in this submission referred to the documents as “ECD (Feb. 2020)” and “ECD (Sep. 2022)”). - Relevant information should be accessible: To fully assess whether the evidence has been taken into account and the ECD provides a reasonable interpretation of the evidence, the stakeholders and the public would need access to all the relevant information. However, the ECD (Sep. 2022) for

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Consultation on the evaluation consultation document – deadline for comments 5pm on 25 October 2022. Please submit via NICE Docs.

	example does not report the final QALY gain or how the economic model has been adjusted in detail (see comments regarding cost-effectiveness, above). - Changes in the narrative of the procedure: (1) On slide 7 of the presentation (issued Sep 2022) of the committee meeting held 6 July 2022, it is stated under ECM3 Mar 2019: "Appraisal paused to give stakeholders an opportunity to explore further ways to obtain evidence". This information is incorrect: The reason given to the stakeholders (and stated on the website under the "timeline" section) to pause the appraisal in May 2020 is the COVID-19 pandemic. In June 2020, the restart of the appraisal was announced, but no further information on the timeline was provided at that time. Formal activities were only resumed in December 2021, when the stakeholders were invited to a workshop was organised by NICE. Without clear information on the timeline, it is not possible, for example, to plan and conduct bigger studies to generate evidence. . - The new evidence submitted by the stakeholders in March 2022 was assessed by the evidence review group (ERG) Southampton Health Technology Assessments Centre (SHTAC). Regrettably, the stakeholders were neither informed nor involved in the assessment and had not possibility to provide feedback and information and/or clarify open questions before the committee meeting held on 6 July 2022, although they offered to provide their assistance. The stakeholders for example would have noticed that the entire submission of new evidence from the British Association of Dermatologists has not been forwarded to the ERG, a mistake that only became apparent one day before the committee meeting held 6 July 2022. Given the delay of the appraisal of already more than three years because of the pandemic (while other appraisals continued…). we think that NICE should do everything in their power to at least now enable a timely process. As patients with EPP living in England have no treatment option, every unnecessary delay and inefficiency is ethically questionable.
6	**NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:** **• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;** **• could have any adverse impact on people with a particular disability or disabilities.** **Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.** <u>Nature of the condition - mutations in ALAS2 and CLPX cause protoporphyria, too:</u> The IPPN would like to make the committee aware that with the current description, a small subgroup of patients could be excluded from the treatment. By stating that: "*Erythropoietic protoporphyria (EPP) is a genetic disorder. It is caused by impaired activity of the enzyme, ferrochelatase."* (ECD September 2022, p. 4) other causes for the disease are not considered in the description of the condition. Protoporphyria can also be the result of gain-of-functions mutations in the genes for delta-aminolevulinate synthase 2 (ALAS2, the first enzyme of the heme biosynthetic pathway) and caseinolytic mitochondrial matrix peptidase chaperone subunit (CLPX, a chaperone of ALAS2). Both genetic defects cause a similar clinical presentation regarding the phototoxicity as loss-of-function mutations in the gene for ferrochelatase.

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Afamelanotide for treating erythropoietic protoporphyria [ID927]

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	In case these patients with protoporphyria are not mentioned in the ECD, there is a risk that they might become excluded from the treatment and unlawfully discriminated in case afamelanotide is made available by the NHS. References: Whatley, S. D., Ducamp, S., Gouya, L., Grandchamp, B., Beaumont, C., Badminton, M. N., ... & Puy, H. (2008). C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. The American Journal of Human Genetics, 83(3), 408-414. Yien, Y. Y., Ducamp, S., van der Vorm, L. N., Kardon, J. R., Manceau, H., Kannengiesser, C., ... & Paw, B. H. (2017). Mutation in human CLPX elevates levels of δ-aminolevulinate synthase and protoporphyrin IX to promote erythropoietic protoporphyria. Proceedings of the National Academy of Sciences, 114(38), E8045-E8052. <u>Access to afamelanotide is an ethical imperative:</u> *"The committee recognised that phototoxic reactions cause serious and severe symptoms, including intense pain and extreme tiredness, that last for days."* (ECD Sep. 2022, p. 6) The committee in the ECD (Sep 2022) acknowledged that treatment with afamelanotide brings the patients in the normal range for light exposure which is only possible if under treatment the symptoms as described above are no longer present. The committee further accepted that the Quality of Life normalised under treatment and that the associated utility values for patients under treatment are comparable to the utilities found in the general population. **In our opinion, a treatment that is accepted to make such a difference to the patients' lives must be made available to them**, as this would promote equality of opportunity by enabling a normal life, eliminate unlawful discrimination and fosterer good relations between people with particular protected characteristics and others. Even more so, as (1) the costs for afamelanotide are considerably lower than the costs for other highly specialized technologies recommended for funding, and (2) the ICER of 121.233 GBP is now very close to the threshold for cost-effectiveness.
7	
8	

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Dermatologists (the BAD)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Has all of the relevant evidence been taken into account?** Thank you. The BAD is unaware of further relevant evidence to take into account other than that presented in the Evaluation Consultation Document September 2022.
2	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** The BAD is appreciative of the further time and attention paid to the potential funding of this breakthrough drug in the treatment of the disabling disorder, EPP. The BAD notes a major change in the calculations made by NICE on the cost effectiveness of afamelanotide in EPP. NICE now finds that the ICER based on their original model, which ranged between £1.34m and £1.73m per QALY gained, were unlikely to be plausible. Taking into account evidence that has been supplied by the patient organisation IPPN has led NICE to revise the ICER estimate to between £121,233 and £231,320 per QALY gained. Specifically, NICE now considers that a plausible ICER is £121,233 per QALY gained as this scenario includes its preferred assumption, i.e. with reference to EQ-5D data. This is close to the £100,000 threshold per QALY required for funding. As there is acknowledgement by NICE that remaining uncertainties remain due to the challenges of sufficiently capturing the benefit of this treatment in EPP (described through many strands of evidence including strong patient testimony), and that the cost-effectiveness analyses for afamelanotide are very challenging (e.g. 1, page 3), the BAD respectfully asks NICE to now speedily fund afamelanotide for the treatment of EPP.
3	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** *"Afamelanotide has a marketing authorisation in the UK under exceptional circumstances"* (3, page 4). Can NICE kindly explain what they mean by this (presumably this relates to Scotland although this is not specified?)
4	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** EQ--D data should be corrected to EQ-5D data (4.20, page 15)
5	**Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?** The BAD clinical experts agree that the anti-oxidant effect of afamelanotide could only be speculated upon, thus in the sentence (4.4, page 28, third sentence from bottom of page), we would propose adjusting to: *"…the clinical experts describe how the protective effects of afamelanotide (melanisation and presumed anti-oxidant effect) need time to build up after the first implant and persist for a period of time after the last implant."*
6	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** While the new evidence that was taken into account led to the above (2) revision of the ICER calculation, other new evidence was dismissed. Several new strands of evidence were provided including from a prospective, post-authorisation observational study, retrospective chart review and a longitudinal case-control study (4.30, page 21-22).

Please return to: **NICE DOCS**

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	Despite some limitations of the data, it was disappointing that NICE felt they could not take into account any of these data on the benefits of afamelanotide treatment in EPP, particularly in view of the acknowledged difficulties in capturing benefits in this disability (1, page 3 and 4.32, page 23). *"The committee noted that it was not possible to quantify the underestimation".* (4.38, page 27)
7	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** The BAD has provided information and responses to NICE on this topic in 2016, 2017, 2018, 2019 and 2022 and during several instances over these years has strongly supported the proposals for a managed access agreement (MAA), if NICE should not feel that there is adequate evidence for drug funding outright. The BAD regrets the years that have passed without access to this treatment by patients in England (despite its availability for many years in several other countries) and continues to strongly recommend this route if full funding cannot be recommended by NICE (point 2 above). As acknowledged by NICE, there is a wealth of evidence that the drug is effective in this complex disability, and moreover, the overall financial outlay is relatively low. Respectfully, we ask that NICE reach the logical solution to progress to an MAA based on current evidence, without further delay. Such an MAA would, naturally, incorporate data on benefits of the treatment.
8	**Are the provisional recommendations sound and a suitable basis for guidance on the use of afamelanotide in the context of national commissioning by NHS England?** NICE specified that the Innovative Medicines Fund (IMF) had launched since afamelanotide was last considered and that it requires the company to make a new proposal for commercial access in line with this. The content of this remains a private matter between NICE and the company and the BAD is therefore unable to comment on this, but trusts that incorporation of the IMF procedure would occur in a manner enabling a positive outcome.
9	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The aspect of the specific disability of EPP continues to cause difficulty in the appraisal of the impact of EPP and its treatment, including considerable challenges in evidence collection. Therefore, there are still aspects that need particular consideration to ensure there is no discrimination of this patient group on the grounds of their disability.

Insert extra rows as needed

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Evaluation consultation consultation comments

User	Consultation Name	Document Name	Comment

Respondee 1	Evaluation consultation	Afamelanotide for treating erythropoietic protoporphyria	I don’t understand why a treatment that removes almost all symptoms of EPP is not recommended? As a XLEPP patient I would do anything to have this treatment. To the point me and my family have considered moving countries for me to gain access. That’s how life changing it would be for me. Also, as the annual treatment costs per person is not that high (48080 GBP with four implants per year, and 36030 with three), it is ethically questionable why the treatment is not made available. Treatments previously recommended by the same committee have list prices of 125000 to > 600000 GB? For me, and many other people we are struggling to understand why it is still not recommended? XLEPP affects my everyday life. I have to constantly think about if I’m going to be in visible sun light. For example popping to the shop, sitting in the living room near windows, driving in the car, reflections from mirrors, walking in other peoples shadows. I struggling with depression and anxiety as I feel I am so different to everyone around me and they don’t understand how I feel and they can live normally. I often feel that others think I’m being over the top, which is a horrible way to feel. I’ve just had a baby, he is 12 weeks old and I’ve just found out he has inherited XLEPP from me. I don’t want him to live the same childhood I had, he’s deserves a normal life, like I did and still do, and so do all of the other patients. If there is something that can make this happen, we should be allowed it.

Respondee 2	Evaluation consultation		The potential benefits of this treatment are undeniably positive for me as an EPP sufferer. The thought of not having to be concerned by the weather forecast every day is so exciting as currently my life is dependant on what the weather is like. If the forecast is for a sunny day, any plans I had need to be cancelled and I spend the day sitting indoors. The affect this has on my mental health is huge and especially after a period of prolonged warm weather, I find myself becoming miserable and depressed. On the physical pain I feel on the occasions I do need to go outside on a hot day, they are unbearable and I can't do anything but sit in front of a fan in a cold dark room. The only way I can describe it is if you imagine your blood is boiling under your skin. There's no way to cool it down and all I can do is scratch at the burnt areas until its raw which actually makes it worse. I tell people to think of how it feels when you open the oven and the heat hits your face, it's like that but constantly all over your body. Although I was unable to join any of the trials, the stories I heard from people who did filled me with hope as I heard how this treatment literally changed their lives. The ability to live a 'normal life' is something that right now, myself and people with EPP can only dream of. The ability to go to the shop if we want to, see friends or family during the summer or just sit near a window are things that so many take for granted but for us, it's all we want to do and this treatment gives us the potential opportunity to do just that.

Respondee 3	Evaluation consultation	Afamelanotide for treating erythropoietic protoporphyria	It is not clear to me how this conclusion has been reached. I have talked to many EPP patients before and during Afamelanotide treatment and can attest to the fact that this is a life changer for them. They become functioning and productive, contributing, members of society under treatment. The patients I know personally were hardly able to handle any sunlight at all, and under sceness treatment have been able to tolerate the sun just as well as me, who doesn't have EPP. This effect is definitely measurable and has in the past been measured and published. So I ask you kindly to reconcider and adjust your recommendation.

Respondee 4	Evaluation consultation	Afamelanotide for treating erythropoietic protoporphyria	I don’t understand why a treatment that removes almost all symptoms of EPP is not recommended? As a EPP patient I would do anything to have this treatment, I would literally give an arm to feel normal, like other human beings. Why am I not allowed to feel normal, why would you not consider my overall health? My happiness? It would mean the world to me to be able to watch my children compete in their sporting events, to be able to walk my dog, to be able to drive to a shop, to be able to even hang my wash up? To avoid abuse I get in the streets for walking around, fully clothed, hiding under an umbrella in 30 degrees heat? To not swell up like and be in constant pain with sleepless nights simply because I got caught out? That’s how life changing it would be for me. Also, as the annual treatment costs per person is not that high (48080 GBP with four implants per year, and 36030 with three), it is ethically questionable why the treatment is not made available. Treatments previously recommended by the same committee have list prices of 125000 to > 600000 GB? For me, and many other people we are struggling to understand why it is still not recommended? EPP affects my everyday life and the life of my family and friends. I have to constantly think about if I’m going to be in visible sun light. For example popping to the shop, sitting in the living room near windows, driving in the car, reflections from mirrors, walking in other peoples shadows. I struggling with depression and anxiety as I feel I am so different to everyone around me and they don’t understand how I feel and they can live normally. I often feel that others think I’m being over the top, which is a horrible way to feel. If there is something that can make this happen, we should be allowed it.

Respondee 4	Evaluation consultation	Afamelanotide for treating erythropoietic protoporphyria	I don’t understand why a treatment that removes almost all symptoms of EPP is not? As a EPP patient I would do anything to have this treatment, I would literally give an arm to feel normal, like other human beings. Why am I not allowed to feel normal, why would you not consider my overall health? My happiness? It would mean the world to me to be able to watch my children compete in their sporting events, to be able to walk my dog, to be able to drive to a shop, to be able to even hang my wash up? To avoid abuse I get in the streets for walking around, fully clothed, hiding under an umbrella in 30 degrees heat? To not swell up like and be in constant pain with sleepless nights simply because I got caught out? That’s how life changing it would be for me. Also, as the annual treatment costs per person is not that high (48080 GBP with four implants per year, and 36030 with three), it is ethically questionable why the treatment is not made available. Treatments previously recommended by the same committee have list prices of 125000 to > 600000 GB? For me, and many other people we are struggling to understand why it is still not recommended? EPP affects my everyday life and the life of my family and friends. I have to constantly think about if I’m going to be in visible sun light. For example popping to the shop, sitting in the living room near windows, driving in the car, reflections from mirrors, walking in other peoples shadows. I struggling with depression and anxiety as I feel I am so different to everyone around me and they don’t understand how I feel and they can live normally. I often feel that others think I’m being over the top, which is a horrible way to feel. If there is something that can make this happen, we should be allowed it.