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. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - **Clinuvel UK**
   - **British Porphyria Association**
   - **International Porphyria Patients Network**
   - **British Association of Dermatologists (BAD)**
   - **Royal College of Pathologists**

3. **Comments on the Evaluation Consultation Document received through the NICE website**
   - **Additional Web Comment**

   Please note that a "no comment" response was received from the Department of Health. The Royal College of Physicians endorsed the comments submitted by the British Associated of Dermatologists (BAD).

4. **Additional paper** - Clinuvel Budget Impact Assessment

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Afamelanotide for treating erythropoietic protoporphyria [ID927]

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD 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 evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
Clinuvel	**Appendix 1 – Responses to ECD** **1. Has all of the relevant evidence been taken into account?** SCENESSE® (afamelanotide 16mg) is the first product globally to have gained approval for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). EPP is a rare metabolic disorder which causes phototoxicity (anaphylactoid reactions and burns) when patients expose themselves to light. We have set out in detail below our concerns that NICE has not taken into account all the relevant scientific evidence in its ECD. See also the comment in Appendix 2 regarding the apparent omission by NICE within the Evaluation Committee (hereafter the "Committee") papers of the document appended to the Company's correspondence of 06 November 2017. 1.1 Evaluation of clinical effectiveness The ECD raises questions as to the clinical effectiveness and benefit of SCENESSE® to EPP patients and does not appear to have taken the evidence provided by the Company, the patients or the expert physicians into account. Specific examples of statements within the ECD which show that NICE has failed to take into account evidence regarding the effectiveness and benefits of SCENESSE® are set out below, together with the Company's comments. *"Clinical trial results suggest that afamelanotide may be effective. But it's unclear how effective it is, whether the effectiveness varies from person to person and how it affects quality of life."* (Section 1.2) (emphasis	Comment noted. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). Please see section 4 of the Final Evaluation Document (FED) for the committee's consideration of the evidence.

Consultee	Comment	Response
	added) However, the lack of clarity alleged by the ECD seem incomprehensible since expert clinical and patient evidence and compassionate use have shown the effectiveness of the drug and the impact on patients' quality-of-life (QoL), which were recognised by the EMA and the EU Commission in granting marketing authorisation. This expert clinical and patient evidence has been discussed in detail within the European Public Assessment Report (EPAR). *"… committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials."* (Section 4.7) (emphasis added) There is sufficient evidence to show that both clinical and patient experts know that the clinical benefit seen is greater than that reflected by conventional or clinical trial analyses and evaluation, rather than simply believing this to be the case. *"The committee noted that patient testimony about afamelanotide reported much better outcomes than the clinical trials... The committee considered the possibility that these testimonials were not reflective of all patients' experience on afamelanotide because it had not been presented with any data indicating that these were a representative sample of everyone who had had afamelanotide. The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear."* (Section 4.8) (emphasis added) These patients and clinical experts were selected and considered representative by the EMA Committee for Medicinal Products for Human Use (CHMP) during its review process and NICE has no evidence on which to consider this not to be the case. In addition, the Company has had no influence over the number and type of patients and clinical experts who were invited. *"… it noted that it had not been provided with any data showing how the reduction in phototoxic reactions seen with afamelanotide affected peoples' ability to work or study. The committee was aware that the company had provided exploratory analyses on loss of earnings associated with EPP, but it was unclear what the data underpinning the company's assumptions were. The committee concluded that afamelanotide would have an impact beyond direct health benefits but that the extent of this impact was unclear."* (Section 4.19) Paragraph 43 of the NICE HST Guidance[1] states that in NICE's deliberations they must take into account the	

1. ID927 Afamelanotide ECD comments table final to PM [redacted]

Consultee	Comment	Response
	impact of the technology beyond direct health benefits. Additionally under paragraph 41 of the Guidance the Committee is required to consider "any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition". Therefore, by concluding that, due to lack of quantitative data, the impact beyond direct health benefits is unclear, it demonstrates a failure to take into account the relevant qualitative evidence. *"The committee noted the possibility that deeply ingrained light avoidance behaviour may have influenced the trial results. However, it was aware that this alone may not explain the huge gap between expert testimonies, anecdotal evidence of those present at the meeting and the trial results."* (Section 4.20) While the Company agrees that there is a difference between the efficacy demonstrated in clinical trials and the overwhelming clinical effectiveness derived from the clinical statements, reports and testimonies of patient and clinical experts, the Company has consistently noted that there is a lack of scientific tools and instruments to fully measure and capture the impact of EPP, light deprivation, and/or a photoprotective treatment. Indeed the EPAR clearly noted that the lack of scientific tools and instruments was a determinant factor in the product's final approval under exceptional circumstances (EC), since it was not possible to generate the clinical evidence required. Further, the EMA CHMP convened an Ad-Hoc Expert Group Meeting in 2014 as part of the marketing authorisation assessment procedure (which is discussed at length in the EPAR) and which recognised the challenges posed in evaluating EPP and the collection of evidence, concluding: *"In this setting the randomised controlled trial appears to be a less effective tool for determining treatment effects… In all 5 clinical trials of various designs it has proven impossible to accurately record the increased clinical freedom and loss of risk aversion reported by the majority of patients and physicians. Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin. It is also conceivable that the complexity of the EPP patients (sic) behaviour and the dependence of phototoxicity with environmental factors in real life differ to such an extent that the actual benefit cannot be captured in conventional clinical trial designs…"* (Pages 89-90). In addition to the above specific points, significant submissions were made by the Company regarding the clinical benefit provided by SCENESSE® to EPP patients who received it that appear not to have been fully taken into account. A marketing authorisation granted under exceptional circumstances, by its nature, shows that despite the marketing authorisation holder's inability to collect the comprehensive data normally required to obtain a marketing authorisation (i.e. data to demonstrate the safety and efficacy profile of an authorised	

Consultee	Comment	Response
	product in its target indication) the medicinal product is nonetheless considered efficacious and to have an acceptable safety profile. While the ECD notes the EC approval (section 3.1), both the Evidence Review Group (ERG) and the Committee have failed to take its significance into account in all of their documentation, to acknowledge the uniqueness of the EMA CHMP conclusions, or to incorporate the evidence that the EMA CHMP used in their review of SCENESSE®. The ERG, Committee and ECD also fail to recognise that it would be unreasonable to request or expect the Company to provide data which are impossible for the Company to obtain due to the ethical and scientific limitations around the conduct of clinical studies (which the EMA CHMP recognised and accepted). This is particularly the case in light of the fact that the EMA concluded that there was sufficient evidence to grant a marketing authorisation under exceptional circumstances. In addition, given the ruling of the Court of Appeal in the case of Servier v NICE[2] it would be a misapplication of NICE's powers to re-open the conclusions of the EMA CHMP without a valid justification for doing so. Therefore, NICE must adequately and properly take into consideration the evidence considered by the EMA CHMP regarding the effectiveness and clinical benefit of SCENESSE®. [1] Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes [2] *R (Servier Laboratories Limited) v National Institute for Health and Clinical Excellence & Anr* [2010] EWCA Civ 346 (on appeal from QBD Administrative Court). The Court of Appeal held that a decision of NICE should be quashed on the grounds that it lacked adequate reasoning and the court had 'grave concerns' about its rationality. In particular, the decision of NICE not to take into account a particular clinical trial when assessing the effectiveness of Protelos was quashed.	
Clinuvel	1.2 Quality of life data and tools The ability to capture and quantify the impact of EPP on patient quality of life is discussed in the ECD. *"… the company had developed a condition-specific quality-of-life questionnaire called the EPP-QoL, but that this had not been validated… The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that people with the condition and their clinicians report as important. It also concluded that, without appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture any treatment benefits with afamelanotide."* (Section 4.9) *"The committee noted that the ERG considered that, although not perfect, the DLQI addresses some factors that impact on the quality of life of a person with EPP, such as pain and ability to work or study. The committee heard from the patient experts that the DLQI includes questions that are not relevant to EPP… DLQI does not ask anything about exposure to light, unlike the EPP-QoL. Furthermore, the*	Comment noted. See sections 4.10 and 4.11 of the FED.

Consultee	Comment	Response
	company stated that the DLQI does not ask about feelings of anxiety… The committee was also disappointed that available SF-36 data had not been presented by the company because this measure includes questions on fatigue and anxiety that are not captured by the DLQI." (Section 4.10) The focus of the Committee was on the appropriateness and omission of pain, work and study from the EPP-QoL and the preference for the DLQI. However, having taken extensive expert advice in the UK and globally on this point, the Company's clear position is that the DLQI is not appropriate to capture the QoL of patients with EPP. The suggestion that the DLQI may be able to 'address some factors' in capturing EPP is very far from a finding that the DLQI is able to accurately capture the impact of the disease on patients, and thus the impact of treatment. As a matter of fact the DLQI has been deemed unsuitable by the global experts in porphyria to capture the impact of EPP, and this position led to the attempt to develop a disease-specific instrument. The Company's position is that because the DLQI is a short-term evaluation (i.e. discussing "the last week" of a patient's experience) aimed at general skin disorders rather than the severe complexities of the lifelong condition EPP, the DLQI is in no way sensitive enough to truly capture the full impact of the disease - unfortunately, currently no tool/instrument is. It appears that the Committee has not fully taken into account the reasons why the EPP-QoL would be more suitable than the DLQI. The reasons for this are briefly summarised below: • It appears the Committee is taking a contradictory position, as they dismiss the EPP-QoL for supposedly omitting two issues relevant to EPP ("pain" and "work or study") but accept that the DLQI despite its very broad focus on the impact of a patient's skin (EPP is not a skin condition, and the Committee learnt from patients and expert physicians that the restrictions in the disease are largely due to environmental and artificial light exposure) and lack of focus on EPP-specifics. • While "pain" is a clinical symptom of EPP it is relatively rare that an adult patient will actually experience "pain'' since they will have adapted their lives to avoid it. Therefore measuring "pain" will yield no results of any significance, hence why it was not included in the EPP-QoL. Pharmacologically, within the field it is accepted that "pain" is a surrogate description of phototoxicity for which the medical nomenclature is currently lacking. • Anxiety has been dealt with in the EPP-QoL by the inclusion of the question "how often did you feel you were at risk of developing EPP symptoms?"; however, questions on fatigue were not addressed as they have not always been seen as a clinical symptom (as has been the case for many medical	

Consultee	Comment	Response
	conditions) and the EPP-QOL was used prior to patients starting to raise awareness of the issue of fatigue (i.e. pre- 2014). • SF-36 data were gleaned from the CUV017 study by the ERG. The CUV017 study is not considered pivotal by the Company but forms only part of the evidence base; however, to use the SF-36 data from this study alone as a basis for the ERG evidence is not representative of the clinical program or the disease of EPP, nor is it a rational approach. • It is not correct to say that the EPP-QoL has not been validated, since it has been partially validated. The Company has always presented that this tool is partially validated, and this is also stated in the Biolcati et al (2015) paper. Additionally, due to the lack of scientific tools to measure the effects of EPP (as set out above) there is long-standing evidence that standardised tools are inappropriate for quantifying QoL in EPP (see the Rufener, 1987 paper). • Later in the ECD it is noted that DLQI "could capture some of the key aspects of EPP" (Section 4.10), but this is not elaborated on, leaving one to speculate on NICE's rationale for the use of the DLQI and demonstrating a lack of understanding of EPP. Therefore, it appears that the Committee has concluded that the DLQI model would be preferable	
Clinuvel	**2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** The Company is concerned that NICE has not taken a reasonable interpretation of the evidence regarding clinical effectiveness or value for money for the reasons explained in detail below. Had NICE done so it would have reached a different conclusion regarding both the clinical benefit and cost effectiveness of SCENESSE®. 2.1 Evaluation of clinical effectiveness Further to its failure to take account of the evidence regarding clinical effectiveness as outlined in Section 1.1 above, the Committee has gone on to fail to interpret the evidence presented by the Company in line with the conclusions of the EMA CHMP, with examples provided below in Sections 2.1 and 2.5--2.6. The Committee is re-opening the conclusions of the EMA CHMP without providing a valid reason for doing so or acknowledging the evidence provided to it by the Company regarding clinical effectiveness. As explained above, according to the Court of Appeal in the case of *Servier v NICE*, if a regulatory authority	Comment noted. Section 4.6 of the FED explains the role of NICE's committee which is to provide an independent assessment of the benefits and costs of a technology. The EMA's role, on the other hand, is to consider the potential efficacy of a technology in relation to its safety. Therefore it is appropriate for NICE's committee to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making.

Consultee	Comment	Response
	has assessed the data and on that basis granted a marketing authorisation, NICE must justify any departure from it. Therefore, it will not be acceptable for NICE's assessment to be 'similar' to that of the EMA, rather the EMA's conclusions on the data must be accepted by NICE unless NICE can justify, on the basis of evidence, taking a contrary interpretation or departing from it. The ECD notes that: *"The committee noted that its remit included an independent assessment of the benefits and costs of afamelanotide. It also noted that the EMA considers the potential efficacy of a technology in relation to its safety, (sic) The committee, on the other hand, considers the potential benefits ('effectiveness'), costs and uncertainties around recommending mandatory funding of a technology (in this case afamelanotide) within the overall objectives of the NHS to maximise health gain from limited resources. The committee concluded that it was appropriate to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making."* (Section 4.6) NICE's interpretation of the evidence supporting the grant of the marketing authorisation (i.e. the expert physicians' and EPP patients' testimonies) is departing from the interpretation of the EMA. Furthermore, no justification has been provided for NICE doing so. Therefore, following the principle set down in *Servier v NICE* (detailed above) NICE appears to be not only acting unreasonably but also *ultra vires*. In order to assess the cost effectiveness of SCENESSE®, NICE should rely on the real-life evidence provided by the patients and clinical experts regarding efficacy, as there is no other way to appropriately interpret the evidence regarding the effectiveness of SCENESSE® for all the reasons explained above (and in previous correspondence). The ECD also states: "*The committee noted that patient testimony about afamelanotide reported much better outcomes than the clinical trials... The committee considered the possibility that these testimonials were not reflective of all patients' experience on afamelanotide because it had not been presented with any data indicating that these were a representative sample of everyone who had had afamelanotide. The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear.*" (Section 4.8) The Committee was presented with consistent evidence by the Company, patients and expert physicians that most patients and expert EPP physicians reported, anecdotally, a larger clinical benefit than that shown in	The committee agreed that afamelanotide was effective and that the true benefit of afamelanotide had not been quantified. It was aware that its remit was to evaluate the value of afamelanotide, which includes consideration of cost effectiveness in addition to clinical effectiveness. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. See section 4.23 in the FED.

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	clinical trial data, partially due to the lack of scientific tools and instruments available to measure EPP (see Section 1.1 of this document). This also formed the basis for EC approval from the EMA CHMP. It is not reasonable to take an alternative interpretation of the data within the EPAR regarding the value of the expert evidence, not just as evidence of the impact on the patient but also as proof of efficacy of the product. Further, the ECD notes elsewhere that: *"The committee asked if there was any evidence about how the severity of EPP affected outcomes with afamelanotide, and heard there were no specific data on this. However, the clinical experts suggested that, anecdotally, afamelanotide had been effective across the whole trial population"* (Section 4.7) (emphasis added) In its HST guidance NICE recognises the particular circumstances of orphan diseases, including the potential limits regarding the nature and extent of evidence available, and the Committee is required to consider "any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition" (Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, Paragraph 41). Therefore, it is not reasonable for the Committee to interpret the data provided as failing to indicate the representativeness of the patient and clinician testimony. Further, it is reasonable to interpret that whilst the true extent of benefit has not been demonstrated clinically, it is undoubtedly greater than that shown in the clinical trials, as evidenced by patients and healthcare professional testimony. It is noted that the EPAR does take account of the role qualitative data submitted to CHMP played in its evaluation of the efficacy and clinical benefit of SCENESSE® for EPP: *"Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse."* (Page 102)	
Clinuvel	<u>2.2 Interpretation of disease</u> The ECD notes: *"EPP is a cutaneous porphyria, and the major symptom is hypersensitivity of the skin to sunlight and some types of artificial light. This causes phototoxicity (a chemical reaction in the skin), and the skin may become*	Comment noted. The FED has been amended to reflect the comment. See sections 2.1, 4.5, 4.6 and 4.7 of the FED.

Consultee	Comment	Response
	painful, swollen, itchy and red." (Section 2.1) These statements show a clear lack of understanding of the disease by the Committee. Consistent with the Company's submissions, the major clinical symptom in EPP is phototoxicity, which is not a sensitivity to sunlight but a chemical reaction to visible light (Soret Band peaking at 408 nanometers) *underneath* the skin. This lack of understanding is likely to have influenced NICE's interpretation of the clinical evidence provided, in particular in reaching the conclusion that the DLQI is an appropriate tool to measure QoL. The ECD notes: *"… a relatively small but statistically significant increase with afamelanotide in the amount of time a person could spend in daylight without pain, and a decrease in the number and severity of phototoxic reactions"* (Section 4.7), and *"The committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials".* (Section 4.7) During the Scientific Workshop of 23 March 2016, from the submissions of the Company, patients, and expert clinicians and at the Committee Meeting of 24 November 2017 the Committee was made aware of the restrictions EPP places on patients with regards to their ability to expose their skin to light/sun. While the data captured in clinical trials may seem trivial to members of the Committee, the patients and physicians clearly stated that: 1. Even brief light exposure without the risk of phototoxicity presents a significant improvement to patients' quality of life; and 2. The data captured in clinical trials for direct sunlight exposure was a proxy measure, which indicated a potentially greater effect when considered in the context of artificial, indirect (dappled) or reflective light exposure. The attempts to trivialise the increase in the amount of time patients were shown to spend in direct light shows a lack of understanding of EPP and its impact by the Committee, and the failure to give due weight to this evidence shows that the Committee's interpretations of the evidence provided have not been reasonable and decisions made based on the Committee's disease understanding may have been arbitrary in nature.	

Consultee	Comment	Response
	The ECD notes: "*The committee concluded that there is some variation in how long people with EPP can be exposed to sunlight without a reaction, but the range across people diagnosed with EPP in England, and any variation in patient experience of the condition, was unclear because of a lack of data*." (Section 4.5) Throughout its submission the Company has highlighted the variance of the disease and the effect of conditioned behaviour, the priming phenomenon, and prodromal symptoms unique to EPP patients (the latter two were recognised in the Committee Papers but not by the ECD). The inability to quantify disease variance, however, is not due to a lack of data, but rather a lack of scientific instruments and tools to measure the disease. This issue is discussed in Section 1.1 of this document. In other words, it would not be possible (on the basis of current science) to measure any variation in patient experience of the condition, and therefore it is not a reasonable interpretation of the clinical data to expect this to have been possible to provide.	
Clinuvel	2.3 Long term efficacy The ECD raises questions regarding the ongoing clinical benefit of SCENESSE® for EPP patients: *"However, the committee also heard that, in the long-term observational study (Biolcati et al. 2015), there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials."* (Section 4.7) Contrary to this statement, Biolcati et al (2015) states: *"We therefore conclude that afamelanotide treatment strongly improved QoL in these patients, likely due to mitigated light intolerance."* It is unclear how the Committee has come to a contradictory conclusion, and the comment in the ECD does not reflect the Company's minutes of the meeting of 24 November 2017. Therefore the Committee's interpretation of the evidence presented on long-term use and clinical benefit is not reasonable.	Comment noted. The FED has been amended to provide more clarity. See section 4.8 of the FED.
Clinuvel	2.4 Drug mechanism of action The ECD notes: *"Afamelanotide works by increasing melanin in the skin, which makes the skin tan, giving some protection against light damage."* (Section 1.2) The Company would note that afamelanotide *activates* melanin production. Melanin absorbs and scatters light	Comment noted. This description has been removed from the FED. See section 3 for a description of the technology.

Consultee	Comment	Response
	as a filter as well as scavenging free radicals and activated oxygen species, providing photoprotection in EPP patients. Therefore, the tanning effect is a biomarker of the drug, rather than the sole protective element, and so it appears the Committee has misinterpreted and/or failed to understand the true mechanism of action by which the drug works. It is obvious that the Committee has failed to understand the systemic effect of the synthetic hormone on the integument in EPP.	
Clinuvel	2.5 Melanogenesis The ECD appears to raise concerns on blinding in clinical trials based on the pharmacodynamic effect of afamelanotide (melanogenesis). "… *some patients may have known they were having afamelanotide because it caused their skin to tan.*" (Section 4.6) This concern was addressed by the Company in its responses to the ERG and was accepted by the EMA CHMP in the EPAR as not having any impact on the perceived effect of treatment. In short, a skin colour change *per se* would not have led to a change of behaviour as patients would not consider a skin colour change to equal protection. This is in part because beta carotene treatment (a previous proposed treatment tried by EPP patients) would also lead to a skin colour change but did not equate to effective treatment. The EMA CHMP did not consider that unblinding would have biased the study results. Therefore, it is not reasonable for the Committee to diverge from this opinion in its evaluation and interpretation of the evidence provided.	Comment noted. Section 4.6 of the FED explains the role of NICE's committee which is to provide an independent assessment of the benefits and costs of a technology. The EMA's role, on the other hand, is to consider the potential efficacy of a technology in relation to its safety. Therefore it is appropriate for NICE's committee to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making. Taking all evidence into consideration, the committee agreed that afamelanotide was effective and that the true benefit of afamelanotide had not been quantified.
Clinuvel	2.6 Clinical data The ECD notes: "The committee noted that the Good Clinical Practice inspection conducted by the European Medicines Agency (EMA) highlighted concerns with CUV029 and CUV030, including unsatisfactory collection and	Comment noted. Section 4.6 of the FED explains the role of NICE's committee which is to provide an independent assessment of the

Consultee	Comment	Response
	analyses of data." (Section 4.6) The Committee fails to recognise the outcome of the EMA CHMP's decision on the same issue, which is noted in full in the EPAR: *"Due to GCP non-compliance the efficacy data from these trials were not considered pivotal for the assessment. However, as pointed to by the Applicant there is an unambiguous trend for a positive effect (primary endpoint) in all these two clinical trials CUV029 and CUV030 (and in CUV039, see below). The effect size in the trials appears to be small, but a beneficial effect seems apparent."* (Page 85) Additionally, the EPAR states: *"Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse."* (Page 102) Therefore, the EMA CHMP were reasonably convinced the trial data showed the effect of SCENESSE® and that this effect on EPP patients was positive. Again, in line with the Servier v NICE decision, it is not reasonable for the Committee to raise the issue of GCP compliance in clinical trials without acknowledging that the clinical trial results and trends were in line with the conclusions of the EMA CHMP, or to misinterpret the GCP issues as having an effect on the demonstration of efficacy.	benefits and costs of a technology. The EMA's role, on the other hand, is to consider the potential efficacy of a technology in relation to its safety. Therefore it is appropriate for NICE's committee to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making. No change has been made to the FED. Taking all evidence into consideration, the committee agreed that afamelanotide was effective and that the true benefit of afamelanotide had not been quantified.
Clinuvel	<u>2.7 Commercial in confidence information and intellectual property</u> The ECD notes the Committee's disappointment that the Company considered its model to be commercial in confidence (Section 4.11). The Company noted in correspondence to NICE that the Company: "… has focused more than a decade of R&D efforts on SCENESSE® (afamelanotide 16mg) as the first ever therapy for the ultra-orphan indication erythropoietic protoporphyria (EPP). The Company spent more than 2.5 years developing the DALY model for EPP which, per your correspondence of 10 October, is indeed novel. As a single product company, the DALY model forms part of our intellectual property and the company is not in a position to enable its publication in full." During the Committee meeting of 24 November, the Company reiterated that the model forms part of its intellectual property and that its reliance on a single commercial product after more than a decade of development meant it was reasonable to maintain confidentiality of the model. This is a legitimate and	Comment noted.

Consultee	Comment	Response
	important position for the Company to take, and not one that would have any impact on the interpretation of the relevant data by the Committee, nor would it be reasonable or appropriate to treat it as such.	
Clinuvel	2.8 Economic model (value for money) The ECD notes on several occasions its preference for models other than those proposed by the Company, for example: *"The committee noted, however, that it could consider non-reference case methods alongside those in the reference case if there is a strong case for it. However, it was not persuaded by the theoretical argument for preferring an analysis based on the DALY to one based on the QALY. In addition, the committee considered that it had not been provided with evidence that the data on which disability was assessed were more robust than the data on utility."* (Section 4.12) The Company notes that there is a lack of guidance as to when non-reference models should be accepted, resulting in non-transparent and arbitrary decisions being made on this matter by NICE. Further, the Company clearly outlined in its correspondence to NICE that the use of inadequate tools by the ERG to develop a QALY model was invalid and unreasonable, consistent with the lack of scientific tools and instruments available to measure EPP (see Sections 1.1-1.2 of this document). Further, the Committee notes in section 4.12 of the ECD that its preference for the ERG model has little bearing on the overall use of DALYs vs QALYs, despite the ERG model then arriving at significantly higher ICERs than those proposed by the Company (i.e. the difference between £1,785,957 and £278,386). As an underlying rationale for the Committee's final recommendation, the Company would argue that this is not a reasonable conclusion. The ECD notes: *"The committee considered that this approach provided a more direct link between quality of life measured in patients in the clinical trials and the modelled benefits, and with fewer assumptions than the company's proxy-condition base-case approach."* (Section 4.14) Despite acknowledging that the quality of life measured in patients in clinical trials does not reflect the actual impact of either the disease or its treatment due to a lack of scientific tools and instruments available to measure patient quality of life, the Committee takes no measures to mitigate this in its approach, rather preferring to adopt the ERG models as "more plausible". To acknowledge and yet ignore that the evidence being selected and relied upon is arbitrary, and the preference for the ERG model and the interpretation of	Comment noted. A simple adaptation of the company's DALY model to QALYs results in an ICER of £278,386 per QALY gained, comparable to £278,471 per DALY averted. See sections 4.13 and 4.14 in the FED. Using the company's preferred proxy condition (but based on utility rather than disability weights from the literature) resulted in an ICER of £1,726,802 per QALY gained, comparable to the ERG exploratory base case (using DLQI) assuming 4 implants. See section 4.11 of the FED for the discussion on DLQI and EPP-QoL. The company's approach using EPP-QoL, which included stratification of scores into mild, moderate and severe disease, and the use of a proxy condition potentially resulted in more uncertainty around the final estimates, even if the questionnaire itself was more responsive to changes in the condition. The

Consultee	Comment	Response
	economic value on that basis is not reasonable in the context of EPP or the findings of the EMA CHMP. The ECD notes: *"The clinical experts stated that they expected the implants to be used from around March to October in England, meaning that 4 implants would be used, but that some people may not need the maximum number. The committee noted that the company had provided an estimate of the average number of implants people with EPP may have, but has provided no detail on how this average was determined and whether it was generalisable to people using afamelanotide in clinical practice in England."* (Section 4.16) Appendix 1 to correspondence sent to NICE on 02 October 2017 (included in the Committee Papers) clearly outlines the rationale for the average number of implants used in the Company's model: *These data don't originate from or reflect data on the average number of implants per year from clinical studies, but originate from CLINUVEL's experience in distribution of the product in a compassionate use/expanded access context and also commercial distribution of SCENESSE® in EPP (i.e. 'real world' use).* Per table A2 of the CS: *Average dose of 2.2 implants per year seen in treatment to date*. Per section 12.1.5 of the CS: Average [redacted] implants per patient per annum: represents average seen in expanded access and commercial distribution of the drug to date across the expected EPP patient population. Per section 12.4.2 of the CS: The base case is calculated according to the predicted number of afamelanotide implants received per year (n=[redacted]) according to CLINUVEL data obtained from conditions of use of the product to date. (CLINUVEL submission to NICE 02 October 2017) It is unclear why the ECD has not acknowledged this and it is not reasonable for such evidence to be omitted. It is also not reasonable to reach a conclusion on economic value based on a misinterpretation of the data regarding implant use.	committee considered that the DLQI may not be fully applicable to EPP. However, it thought that the DLQI could capture some of the key aspects of EPP that people with the condition report affect their quality of life, and allow for a more robust estimation of utility values. Section 4.18 in the FED has been updated to reflect the comment on number of implants.
Clinuvel	**3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** In its recommendation the Committee notes that "it was unlikely that afamelanotide would be considered a	Comment noted. Please see the FED for committee's full

Consultee	Comment	Response
	cost-effective use of NHS resources". By misunderstanding the mode of action of SCENESSE® and by failing to take into account all of the evidence provided to the Committee and its unwillingness or inability to interpret the lack of scientific tools and instruments available to quantify EPP or the impact of treatment, the recommendation proposed is not a sound or suitable basis for guidance to NHS England. The Company respectfully requests that the Committee reconsiders all the relevant evidence before the meeting on 20 February 2018.	deliberations.
Clinuvel	**Appendix 2 – Comment on Committee Papers** The Committee Papers are consistent with the Company's comments during the Committee meeting of 24 November 2017. However, it is unclear to the Company why NICE chose not to include the document appended to correspondence of 06 November 2017 in the Committee Papers as this document summarised the Company's position to NICE, including regarding use and cost of the product. A failure to include this document in the Papers suggests it was not supplied to the Committee and, inexplicably as an essential document, no rationale was given for its omission. If the document was supplied to the Committee it should, in the interests of transparency, have been disclosed – to the extent possible – as part of the Committee Papers on NICE's website. A redacted version of the document was provided to NICE on 12 December 2017 for this purpose.	Comment noted. NICE believes that the omission of the document from the committee papers (in advance of the first meeting) did not impact the committee's decision as all the material within it was also contained in other documents. The document was presented to the committee in advance of the second meeting.

Comments received from commentators

No comments received

Comments received from patients and professionals

Commentator	Comment	Response
British Porphyria Association	Patient testimonies Para 4.8 concluded that there was a 'substantial dichotomy between the patient/clinical expert testimony and the trial outcomes, and the true extent of benefit was unclear.' In the same paragraph, NICE queries whether the positive experiences of Afamelanotide are representative of most of those on the trial. Although trial data in the UK is limited, it is evident from qualitative data that very many EPP patients on the trials benefited tremendously from Afamelanotide. **Patient experience is compelling and should be listened to. It should not be underestimated simply because it does not fit the standard criteria on clinical effectiveness.** This data is supported by testimony from UK clinicians who observed changes in patients first-hand (para 4.7). By allowing patients to spend longer in the light, Afamelanotide is reported to be extremely helpful in reducing episodes of pain, fatigue, social alienation and other symptoms of EPP. It has been variously reported as 'life changing' or a 'miracle'. One EPP patient from the UK, who took part in the trial, said: *"Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to switch on the TV or look at your phone because every time you do you feel like you are on fire. Imagine not being able to do your job because the office lights cause you pain.* *That is my day, every day, not just in the summer, but even in winter. Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. I took part in a clinical trial for Afamelanotide. My life changed. I went out of the house in shorts and t-shirt, I sat in the sun, I had the best year of my life. I went from suffering to enjoyment with this treatment! I could spend hours out in the sun without pain for the first time in my life. Now I'm back to hiding, avoiding things, I can't even take my children to school without wearing hat, coat and gloves."*	Comment noted. See section 4.9 of the FED.
British Porphyria Association	Continuation of treatment despite considerable expense The draft recommendations do not recognise the fact that international EPP patients, who have been on Afamelanotide for many years, have travelled considerable distance (at significant cost to themselves) in order to continue receiving the treatment (Biolcati et al. 2015 [1]). We would also request that NICE further consider	Comment noted. See section 4.9. The committee appreciated the compliance rate was high but noted that it was not a quantifiable marker

Commentator	Comment	Response
	the fact that the vast majority of patients who have had Afamelanotide available to them do not cease taking the treatment. This can only be explained by the treatment making a marked difference to their quality of life. *"Ten minutes passed, then 20, 30, 40 minutes and more in the sun without the typical painful symptoms! After over 40 years with the illness, I finally have something against EPP… this treatment changed my life!"* *"For the first time in my life I could accompany my daughter to an athletic competition – and she has won!"* *"For the first time I have experienced how pleasantly warm the sun can feel."* *"Last summer a miracle occurred – I took part in the Afamelanotide clinical trials – for the first time in over 50 years, I was able to venture to the store without the threat of enduring two days of excruciating pain."*	of effectiveness. The committee agreed that afamelanotide was effective and that the true benefit of afamelanotide had not been quantified. It was aware that its remit was to evaluate the value of afamelanotide, which includes consideration of cost effectiveness in addition to clinical effectiveness. See section 4.23 in the FED.
British Porphyria Association	<u>The cumulative/multiplier effect</u> As recognised in the ECD, there is clearly a dichotomy between trial data and patient testimony (para 4.8), resulting in EPP still being a relatively misunderstood disease. Whilst the pathology is now reasonably well established, measurements of the effects of the condition are still evolving. In response to the various written documentation associated with the consultation, a number of our members have pointed out one main aspect that is possibly missing in the calculations and studies; specifically, the real benefit from Afamelanotide is not simply the extra minutes it allows patients to spend in light. Whilst this is significant and highly beneficial, with even small gains leading to substantial improvements, importantly, there is also a multiplier effect on quality of life. Thus, the studies and draft recommendations do not fully take account of the value in avoiding the lengthy recovery periods that follow an EPP event. Given the hours, and sometimes days, taken to recover from an EPP episode, those additional minutes and hours in the sun are not simply the sum of what can be done in those hours (albeit an extremely important gain). It is also the additional work and tasks that could be carried out in the many hours that are lost when an EPP event is triggered. If a small difference in exposure time can prevent a significant reaction and be repeated day after day, even small increments of time spent in light add up to very large returns in terms of productivity and quality of life. The relationship between extra time in the sun and opportunities to the patient is not simply a 1:1 relationship. Therefore, the true impact of the gain cannot be assessed by simplified 'time in sunlight' data. Patients may, for example, be able to walk down a shady side of a street, but then need to cross the road, which means exposing themselves to sunlight. Enabling these additional small times in the sun substantially extends how far	Comment noted. The committee fully considered the testimonies received from patients and was convinced that patients valued the benefits of afamelanotide. However this benefit could not be quantified and the size of benefit remained uncertain. See section 4.9.

Commentator	Comment	Response
	they can go. The ability to withstand a small extra time in the sun also means that EPP patients are able to withstand considerably longer periods in cloudy daylight or even, for some patients, in artificial light. For one of our young adult members in particular, this could be life-changing. He has difficulty attending educational establishments due to pain caused by artificial light.	
British Porphyria Association	Wider impacts: EPP often has considerable effects on future prospects of affected patients. Learning can have to be curtailed, and career options limited. *"My son is doing incredibly well and will be graduating next month from college with his degree in physics! This would not be possible were it not for the protective, life changing effects of Afamelanotide. Two years ago we feared for our son's life as he was in such a dark place due to the cruel and painful effects of EPP. At that time, he was on academic probation and had to go on meds to control his anxiety. Today, he is a happy, healthy and vibrant member of the student body at his college…"* Another illustrative example is a young adult member who had to give up part-time employment in a cafeteria after the building was modernised with a design that included large expanses of mirrored walls. For this person the light in that building has become intolerable to bear for any length of time – the value that Afamelanotide could bring to such a case is immeasurable. It is not only the quality of life benefits of the patients themselves which improve. Reports from family members makes it clear that they also suffer when their parent, child or sibling has EPP. For instance, the activities a family undertakes are curtailed by what the EPP patient can withstand. Their pain is also shared with loved ones. The draft recommendations do not fully take into account the costs and impact of this extended impaired quality of life.	Comment noted. See section 4.2 and 4.21 of the FED.
British Porphyria Association	Hidden costs of EPP: Discussion with our membership has uncovered how the costs of EPP can be hidden. The committee recognised that, even across the medical profession, awareness of EPP remains low (para 4.4). The evaluation also recognises that there is presently no truly effective and practicable treatment (para 4.2) and that EPP has a severe impact on patient lives (para 4.3). What we feel is missing from the evaluation and associated studies is the existing underlying cost of EPP to patients and the nation. With no effective treatment available, many patients make little ongoing demand on NHS resources. This leads to an under-reporting of EPP episodes as well as a poor understanding of EPP in general. Moreover, despite severe psychological impact there is little or no recognised need, or funded,	Comment noted. The committee concluded that afamelanotide would have an impact beyond direct health benefits but that quantifying this was difficult and the impact would be unlikely to be sufficient to overcome the committee's concerns regarding value for money. See section 4.21

Commentator	Comment	Response
	psychological and mental support for patients. Many simply suffer in silence sparing the NHS significant expense that does not appear in calculations. What psychological support is given is rarely ascribed to EPP. Were these 'true costs' being carried by the NHS at present ascribed accurately to EPP, then the cost per QALY would be lower. We call for this deficiency in data to be acknowledged and for analysis models to be improved before a final recommendation is made. Ongoing improved understanding of a disorder calls for the improvement of existing approaches and the adoption of new ones.	in the FED.
British Porphyria Association	***2. Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?*** No, we believe that the summaries and the criteria used in the recommendations fail to adequately take into account the difficulties in measuring EPP. Problems with measurement The formal trials had as a measure, the extent of sun exposure. While this is currently the only utilised measure, it has considerable limitations. • EPP patients have, over a lifetime, developed a fear of exposure to bright light for any length of time. This behaviour is very hard to unlearn, and takes time. • Patients were not told if they were on the treatment or the placebo, so many would be likely to still be very cautious. • During the trials, there will have been cloudy days or days when other commitments prevented exposure, when they will have recorded zero sun exposure. This is in spite of the knowledge that EPP patients can be strongly affected even on cloudy days. Other difficulties in attempting to measure EPP in the trials include: • In EPP there are usually no visible signs – only reported symptoms – which means results are susceptible to highly variable individual factors. • Seasonal impact of the trials: pain scores tend to be relatively low at the start of trials due to starting in the spring, so the full magnitude of the effectiveness of the drug might be difficult to track. • Current methodologies cannot capture the value of any increased time in light.	Comment noted. See sections 4.8 and 4.9 in the FED.
British Porphyria	**Interpreting the evidence**	Comment noted. See sections 4.11

Commentator	Comment	Response
Association	The draft recommendations note that the committee themselves were concerned (para 4.20) that the ERG's own measures 'were highly uncertain because the benefits of Afamelanotide may not have been fully captured by the DLQI measured in the clinical trials'. Therefore the resulting QALY calculations cannot be seen as reliable or reasonable interpretations of the evidence.	and 4.16 in the FED.
British Porphyria Association	***3. 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?*** No. There are some good points within the document and we are encouraged that NICE notes the severity of the condition and the far-reaching impact it has on the lives of EPP patients and their families (para 4.3). We are also pleased that NICE recognises that EPP was, until recently, a little understood condition (para 4.4). Nonetheless, we feel that the extreme extent and burden of the impact has still to be fully comprehended. We fully appreciate the need for rigorous data and outcomes that can be used in fair comparison against other treatments on the grounds of health economics. We also understand how the conclusion has been derived. Despite this, we feel that the huge gulf in levels of impact between the data as applied in the QALY and the testimonies reported by EPP patients treated with Afamelanotide are too wide to be ignored. The patient reports are backed up by significant differences observed in these patients by recognised clinical experts in EPP. We feel that the qualitative evidence must be taken more seriously until appropriate measurement tools can be designed.	Comment noted. The committee agreed that afamelanotide was effective and that the true benefit of afamelanotide had not been quantified. It was aware that its remit was to evaluate the value of afamelanotide, which includes consideration of cost effectiveness in addition to clinical effectiveness. The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources. See section 4.23 in the FED.
British Porphyria Association	***4. 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?*** We are concerned that until the dichotomy between patient and study data is fully addressed, and a more suitable method for assessing Afamelanotide is recognised by the committee, patients will be disadvantaged by the application of an evaluation model that does not permit true measurement of the level of suffering our members are subject to and the beneficial effects Afamelanotide has on lives of EPP patients. The BPA also considers that without full and proper consideration of the contentious issues that remain, our	Comment noted. The FED has been revised to reflect the comment. See section 4.9.

Commentator	Comment	Response
	patients will continue to suffer from lack of economic opportunity and social isolation, that access to an effective treatment would counteract.	
British Porphyria Association	Our recommendations 1. That on further consideration NICE recommend Afamelanotide. 2. That if the final recommendation is not to approve, this should only be put forward once a consensus can be reached by the range of stakeholders on the methodology that should be applied to measure Afamelanotide's impact on quality of life. 3. That the statement relating to the review date is amended to '3 years, or sooner if significant evidence on the efficacy of Afamelanotide becomes available'.	Comment noted. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations. NICE is keen to hear about any new evidence that becomes available before the time of review (please send information to nice@nice.org.uk). NICE will assess the likely impact of the new evidence on the recommendations and will propose an update to the published guidance if required.
Royal College of Pathologists	**Has all of the relevant evidence been taken into account?** Yes; Due account has also been given of patient testimony, in addition to published clinical trial data. **Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** Yes, though it is noted that the company (Clinuvel) disagrees with some aspects of the assessment and modelling. **Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** Given current financial constraints and pressure on NHS funding, the recommendations appear to be sound and fair I do not have anything further to add as the committee's assessment is extremely comprehensive and detailed.	Comment noted.
International Porphyria Patient Network	As a general comment, the IPPN finds a significant inconsistency between the recognition by NICE that there is a "dichotomy between patient and clinical expert testimony and trial outcomes [sic]" and the fact that NICE insisted on evaluating the afamelanotide treatment by generic assessment methods rather than appropriately taking into consideration the uniqueness of erythropoietic protoporphyria (EPP) and the afamelanotide	Comment noted. The committee was aware that its remit was to evaluate the value of afamelanotide, which includes

Commentator	Comment	Response
	treatment effect. Regrettably, the challenges of assessing the consequences of EPP on patient lives and the efficacy of afamelanotide to manage the condition are largely neglected and NICE's evaluation methods are in stark contrast to those applied by other authorities such as the European Medicines Agency (EMA), who recognised that there are no tools and instruments allowing for a precise measurement of the impact of the disease and the benefit of the afamelanotide therapy. Nonetheless, EMA accepted the positive trends from various clinical trials, the unanimous favourable reports of clinical experts and the testimonies of patients on the benefits of the medicine, and approved afamelanotide under "exceptional circumstances" for treatment of adult patients affected by EPP in 20141. In addition and despite the acknowledgement that EPP is a disease that can have far reaching consequences on the lives of impacted people, NICE essentially minimised and overrode testimonies of EPP patients, as well as reports of clinical experts who describe the treatment as "transformative [sic]" and as a "dramatic step-change [sic]" in the management of this disease.	consideration of cost effectiveness in addition to clinical effectiveness. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.
International Porphyria Patient Network	Has all of the relevant evidence been taken into account? No – The overwhelming evidence from EPP sufferers, who have been under the afamelanotide treatment during the clinical trials or have access to the treatment in other countries and who experienced a dramatic change in the quality of their lives and in their health, has not been taken into account. In Italy, Switzerland, the Netherlands, Germany and Austria more than 200 patients have received afamelanotide, some of them for over 10 years, reporting dramatic benefits from the therapy.	Comment noted. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the ERG. Please see section 4 of the FED for the committee's consideration of the evidence.
International Porphyria Patient Network	Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence? No – EPP is a unique condition and any attempt to measure the efficacy of the afamelanotide treatment using	Comment noted. The committee considered that it had adopted a wide view in considering the

Commentator	Comment	Response
	generic methods does not fairly take into consideration the uniqueness of the condition; EMA, for example, clearly stated that the efficacy of afamelanotide could not be precisely quantified but approved the treatment because of the positive and significant trends from various clinical trials, and because there was clear evidence of clinical benefit reported by patients and healthcare professionals, who consistently reported improvements to patients' quality of life.	evidence base and factored in a range of analyses in its decision-making. See section 4.23 of the FED for a summary of the committee's considerations.
International Porphyria Patient Network	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? No – As stated above the patients' experience of the significant limitations caused by EPP and the dramatic improvement of quality of life experienced by treated patients, also reported by their expert clinicians and emerging from the various clinical trials, have not been given sufficient credit and attention; we regard the quantitative assumptions leading to the recommendations given by the evaluation committee regrettably inadequate since the quantification methods applied are not appropriate in measuring treatment effects in EPP.	Comment noted. See section 4.9 of the FED. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. See section 4.23 of the FED for a summary of the committee's considerations.
International Porphyria Patient Network	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? Sadly, the urgent medical needs of most patients affected by ultra-rare diseases remain unmet. Only a small fraction of ultra-rare disease patients can benefit from effective therapies and EPP patients belong to this fraction of patients, with afamelanotide being the only existing therapy able to manage their disease. We now find that the committee is discriminating against British EPP patients compared to other EPP patients in Europe, who have access to this medicine because it was assessed by recognising the unique nature of the disease and by taking into account patient experience and expert clinician input; the committee unfortunately remains resolute against assessing afamelanotide with the uniqueness of the condition taken into appropriate consideration. The discrimination also occurs by not considering adequate – potentially new if needed – assessment methods which allow evaluating the effectiveness of afamelanotide. Thus, a discrimination occurs in comparison to other patients in general but also to patients who suffer from other ultra-orphan conditions. Equitable medicine access for all British patients, whether the condition is rare or common, is a fundamental principle of the National Health Service. We find that the committee's recommendation could compromise this principle.	Comment noted. The NICE committee's remit is to 'evaluate the benefits and costs of afamelanotide within its licensed indication for treating erythropoietic protoporphyria for national commissioning by NHS England. The committee has fully considered all available evidence and testimonies and adopted a wide view in considering the evidence base. No potential equalities issues have been identified. See section 4.23 for a summary of committee's considerations.

Commentator	Comment	Response
International Porphyria Patient Network	About the uniqueness of EPP EPP is unique in that it features a collection of manifestations and conditions which represent a significant clinical challenge to effectively, objectively and conclusively assess disease impact and management. The following is a list of key features which illustrate the uniqueness of EPP: • The endogenously occurring phototoxic reactions • The related excruciating neuropathic pain which cannot be managed by any medication • The extreme fatigue developing after even relatively mild phototoxic reactions which negatively impacts productivity and, in addition to the severe pain, completely incapacitates patients when the phototoxic reaction is protracted and/or more intense • The debilitating, disfiguring, professionally and socially disabling nature of the disease • The significantly variable environmental conditions which can trigger phototoxic reactions in highly unpredictable fashion (direct light, light through clouds, light reflected from surfaces such as buildings, windows, water, snow, fog and clouds; seasonal cycles and weather conditions, including wind with its considerable negative impact; differences in geographical latitude; etc.) • The absence of accessible and measurable biochemical or other clinical features to objectively assess the magnitude and duration of phototoxic reactions, and consequently the lack of efficacy biomarkers to measure the effect of therapeutic interventions • The mostly invisible nature of the phototoxic reactions, with EPP sufferers being in extreme pain without any apparent external cutaneous signs except when reactions are particularly violent and protracted • The invisibility of EPP leads to a lack of understanding from others, even allegations of malingering, and as a result patients frequently decide to hide and downplay their condition, suffering in silence and alone • And finally, the traumatic experience of phototoxic reactions, particularly during childhood, leads to a deeply ingrained fear of light and of its incapacitating consequences which accompanies sufferers and conditions their behaviour during their entire lifetime, forcing them into an existence of light deprivation with all its physical and mental health consequences	Comment noted. Please see sections 2, 4.1 and 4.2 of the FED.

Commentator	Comment	Response
International Porphyria Patient Network	**Response to sections of the "Evaluation consultation document"** Section 1.2(a): *"Afamelanotide works by increasing melanin in the skin, which makes the skin tan, giving some protection against light damage".* Response: In addition it should be mentioned that afamelanotide has both an anti-inflammatory and anti-oxidative activity, which likely contribute significantly to its effectiveness in EPP. Section 1.2(b): *"Clinical trial results suggest that afamelanotide may be effective. But it's unclear how effective it is, whether the effectiveness varies from person to person and how it affects quality of life."* Response: This statement is inaccurate: In the 2015 Biolcati et al. observational study, it has been shown that only 2.6% of EPP patients treated with afamelanotide have described lack of effectiveness of the therapy in improving their symptoms, while 97.4% of them benefited from the afamelanotide treatment (i.e., 112 of the 115 patients in the study). We interviewed Prof Dr Elisabeth Minder, co-author of the study and director of the National Reference Centre for Porphyrias at the Triemli City Hospital in Zurich, Switzerland; she states: "Our clinical experience treating EPP patients covers more than 30 years, during which we tried every potentially effective therapy for EPP, and they all proved to be inefficacious except for afamelanotide. During the last 12 years we applied afamelanotide to a total of 83 different patients. The very few patients who did not benefit from afamelanotide, stopped treatment after the first dose, i.e., even if afamelanotide is available to them they discontinue treatment, causing no additional ineffective use of resources to our Swiss healthcare system. On the other hand, the extremely high treatment adherence in the great majority of patients, as also highlighted by Biolcati et al., underscores the effectiveness of afamelanotide in improving patient lives. Our clinical experience shows afamelanotide to substantially improve physical and mental health, and quality of life for patients. Those who are moderately affected by EPP can lead a normal to nearly normal life under the treatment, and patients who are more severely affected by EPP experience a significant improvement in quality of life after they receive afamelanotide. Patients consistently call the medicine "life-changing", a "wonder medicine", and they report of a continuous, sustained improvement in their health and lives over time. They could not image going back to the life they had before without the treatment. Unfortunately, some of them did have to experience this as their treatment was interrupted in the year 2016, when we had to re-negotiate reimbursement with Swiss health insurances for every individual of the total 33 Swiss residents we are treating (in addition to Swiss patients we also treat individuals from other nations, including the USA, who regularly travel to Zurich to receive the treatment). This was a very challenging period which was however extremely revealing in pointing out how afamelanotide is essential for patients. For example and as an illustration of the gravity of the situation, as a consequence of light deprivation and the painful phototoxic reactions resulting from treatment interruption one patient required hospitalisation because of exacerbated depression; several other	Comment noted. The technology is described in section 3. Comment noted. Section 4.8 has been updated to clarify this point. The committee believed afamelanotide offers a clinical benefit, but the size of benefit remained uncertain. See section 4.9.

Commentator	Comment	Response
	patients showed signs of depression and had suicidal thoughts; and two patients had to quit their jobs because working conditions exposed them to sunlight and in the absence of treatment they were subject to phototoxic reactions again as opposed to when they were under treatment. Now fortunately, we could successfully re-negotiate reimbursement and patients receive the treatment again and are back to their normal, productive new lives." Additionally, the European Medicines Agency (EMA) summarise the results for all Phase III clinical trials and the second Phase II trial as significant, with verum patients able to spend more time in direct sunlight, and experiencing both less phototoxic episodes and lower maximum pain severity per phototoxic episode (see table on pages 74-75 in the EPAR report). From this collective evidence we conclude that the afamelanotide treatment is clearly and significantly effective and of benefit to EPP patients, and do not agree with the committee's assessment that the treatment may be effective and that it is unclear how effective it is. Sections 1.2(c), 4.10, 4.14 1.2: *"The cost-effectiveness estimates for afamelanotide are all much higher than the range normally considered acceptable for highly specialised technologies. This is despite taking account of the impact on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and that afamelanotide is an innovative treatment."* 4.10: *"The committee discussed the DLQI. It was aware that this is a validated quality-of-life questionnaire, but validated for conditions only affecting the skin, rather than for EPP. The committee noted that the ERG considered that, although not perfect, the DLQI addresses some factors that impact on the quality of life of a person with EPP, such as pain and ability to work or study."* 4.14: *"The committee therefore considered that the ERG's approach may have underestimated the real-life benefits of afamelanotide because these may potentially have been underestimated in the trials, but that it was not possible to quantify by how much. It concluded that the ERG's exploratory modelling approach was its preferred approach."* Response: The cost-effectiveness calculations applied by NICE's evidence review group (ERG) are based on misleading assumptions, in particular as it relates to adoption of the DLQI, which they have used in their calculations. We outline below why the use of the DLQI as basis of a quality of life (QoL) determination in EPP is inappropriate: 1. At least 2 of the 10 questions of the DLQI do not apply to EPP (Q 9&10), which reduces responsiveness/sensitivity. 2. The wording of the DLQI questions does not adequately describe EPP-related symptoms, which	Comment noted. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources. The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

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	leads to uncertainty and irreproducibility in the answers given by EPP patients. 3. The responsiveness/sensitivity of the DLQI has never been validated for the efficacy assessment of a treatment for EPP. The limitations of health status (HS) scores have been elaborated by Hamming & De Vries: They highlight that the World Health Organisation (WHO) working group has defined QoL as "the concept with emphasis on the personal evaluation of functioning in relation to individual and/or cultural standards, values, expectations and goals". Therefore, the perception of disease and treatment should not only be recorded (e.g., by measuring HS scores), but also evaluated by the patient, as Hamming & De Vries conclude: "A true assessment of the impact of illness and the outcome of a treatment can be made only if the perception of the patient as an individual is evaluated properly." This did not occur with the DLQI, a generic tool for dermatological conditions which should never be applied to EPP since EPP is not a dermatological disease. Instead, Biolcati et al. performed a direct evaluation of the afamelanotide treatment effects using the Swiss version of the EPP-QoL questionnaire, an EPP-specific tool, in line with the recommendations of Hamming & De Vries. The patients scored their quality of life directly on a Likert-type scale by answering the question: "Taking your EPP into account, mark the box which best describes the quality of life 'NOW', whereby 0 means the worst possible and 10 the best possible life quality" (Appendix 1 in Biolcati et al.). The outcome of this direct QoL evaluation was the following: The current life quality in untreated and treated adult EPP patients resulted in scores of 4.0 + 2.9 and 8.0 + 1.9, respectively, with the difference having a statistically high significance ($P < 0.001$) (Biolcati et al.). This direct evaluation of the effects of the afamelanotide treatment on personal QoL reflects the highly significant improvement of the perceived general health and life quality reported by EPP patients over a period of 8 years, a considerable timescale and a reality that unfortunately cannot be captured by generic tools such as the DLQI, ineffective and inadequate in EPP. As we do not possess any expertise in health economics, we do not feel we can make any informed comments on the models used for the cost-effectiveness estimates. However, it is apparent that in these models the ERG did not take into account statements by expert clinicians and patients on the transformative and life-changing properties of the afamelanotide treatment (captured in detail in the full Evaluation Report [committee papers]), nor real world evidence such as that reported by Biolcati et al. In fact, the ERG completely minimise and override this important input which translates effectively the abstract improvements emerging from the clinical trials to the actual clinical benefit experienced by patients. The ERG has not adequately taken into consideration the challenges which typically characterise clinical trials for rare diseases; they override the assessment made by the EMA which recognise that "Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease" (page 90 in the EPAR report), and despite this conclusion the ERG insist on applying generic assessment methods clearly inappropriate in EPP; and finally the ERG largely neglects the positive outcomes	

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	and trends that, in spite of all the challenges, do emerge from the clinical trials (e.g., see table on pages 74-75 in the EPAR report). We therefore urge NICE to ensure that a balanced approach be applied to the cost-effectiveness estimates, taking all inputs, trends and limitations into consideration which, it must be stressed, other European national authorities and the EMA have used to decide in order to make afamelanotide available to European EPP patients. As example, we refer here to the comprehensive evaluation carried out by the German Institute for Quality and Efficiency in Healthcare (IQWiG), the German Federal Joint Committee (G-BA) and an Arbitration Board called under the German Pharmaceuticals Market Reorganisation Act (AMNOG), after which a pricing agreement was reached and a reimbursement amount binding for all German state health insurers was set. This outcome was obtained after the German authorities took into account and reviewed all the data and information. This is a process which aims to find a cost-effective solution for all involved stakeholders and takes into objective consideration both the costs of innovative therapies and the long-term sustainability of medicine access to patients. In the case of afamelanotide there has been an evident agreement that all	
	Section 2.1(a): *"Erythropoietic protoporphyria (EPP) is a genetic storage disorder."* Response: EPP is not a "storage disorder". EPP is an inborn error of metabolism leading to accumulation of protoporphyrin IX.	Comment noted. The FED has been revised to reflect the comment. See section 2.1.
	Section 2.1(b): *"This causes phototoxicity (a chemical reaction in the skin), and the skin may become painful, swollen, itchy and red."* Response: We recommend extending this description as follows: This causes phototoxicity (a chemical reaction in the skin with destruction of subpapillary capillaries and perifocal edema), and the skin becomes painful, swollen, itchy and red, and in more severe episodes petechias and skin erosions occur.	Comment noted. The FED has been revised to reflect the comment. See section 2.1.
	Section 4.2: *"Clinical experts stated that beta carotene and narrow band UVB therapy have been tried as treatments to prevent phototoxicity but these are decreasingly used because of lack of clinical effectiveness."* Response: Beside their lack of effectiveness in EPP, beta carotene has been associated with increased risk of death from lung cancer and cardiovascular disease, and UVB exposure is well known to increase risk of developing skin cancer with a delayed incidence of several years. These are additional factors discouraging such treatments whose life-long administration would expose EPP patients to considerable risks to their health.	Comment noted. The FED has been revised to reflect the comment. See section 4.3.

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	Section 4.5: *"The committee concluded that there is some variation in how long people with EPP can be exposed to sunlight without a reaction, but the range across people diagnosed with EPP in England, and any variation in patient experience of the condition, was unclear because of a lack of data."* Response: This is inaccurate since Holme et al. have published data for EPP patients in the U.K. According to this paper the median time for onset of symptoms following exposure to sunlight was 20 min (lower quartile: 10 min; upper quartile: 60 min; range: immediately to 12 h or asymptomatic). We also want to point out that, despite some individual variance in the time it takes for a phototoxic reaction to occur, it is often too late to realise that a severe reaction is underway. The given circumstances might also prevent patients from seeking shelter from additional phototoxic exposure which precipitates a reaction very rapidly, and then the resulting consequences (severe pain, fatigue, incapacitation, etc.) are very similar across patients.	Comment noted.
	Section 4.7(a): "*However, the committee also heard that, in the long-term observational study (Biolcati et al. 2015), there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials."* Response: In the clinical experience of the National Reference Centre for Porphyria in Zurich, Switzerland, led by Prof Dr Elisabeth Minder, co-author of the Biolcati et al. paper, the improvement of the QoL markedly precedes the change in life style. Patients require at least 2-3 years of continuous treatment with afamelanotide until they report a decrease in their fear of light and until they start changing their lives in a positive way, such as by switching to new, typically better compensated employment which might subject them to increased light exposure. Also, we consider the QoL score of about 80% as the maximum score typically achieved in any QoL questionnaire, so that a further increase cannot be expected.	Comment noted. The FED has been revised to reflect the comment. See section 4.8 of the FED.
	Section 4.7(b): "*The committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials*" Response: We reiterate that the real life benefit of the treatment is dramatically more substantial than what may appear from the clinical trials. As key study we refer here to the Biolcati et al. paper, where afamelanotide was applied under routine outpatient clinical conditions over several years, the response rate was 97% and treatment adherence exceptionally high. In addition, there is ample anecdotal evidence from patients beyond	Comment noted. The committee concluded that afamelanotide did offer a clinical benefit, but the size of benefit remained uncertain. See section 4.9 of the FED.

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	those investigated by Biolcati et al. that the benefits of afamelanotide are life-altering and dramatic. Section 4.8: *"The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear."* Response: This is a key issue: The clinical trials measured spontaneous sunlight exposure and not light tolerance, which are often confused. In the data evaluation of the clinical trials the average daily increase in sunlight exposure has been diluted by rainy or cloudy days, or by days during which patients could not expose themselves to sunlight because they were either working indoors or otherwise busy with indoor occupations. Evidently, during those days no sunlight exposure was reported in the diaries used in the clinical trials. This resulted in a statistically significant but small absolute increase of time in sunlight. Such outcome leads to the erroneous perception that the clinical benefit of afamelanotide in EPP is limited. Moreover, there is no effective comparator as we do not know the average daily time of sunlight exposure of a normal population. Taking the widespread vitamin D deficiency in a normal population into account, which could be alleviated by only 15 min sunlight exposure per day, we can extrapolate that the daily average spontaneous sunlight exposure in a normal U.K. population ranges in the minutes and certainly not hours. Unfortunately, we could not find any conclusive scientific data about this. Nonetheless, with this assumption an average gain of 8 min per day (page 102 in the EPAR report) has to be considered as a substantial improvement. Section 4.9(a): *"The committee discussed how quality of life had been assessed in the clinical trials. It noted that the generic short-form 36 (SF-36) and generic skin condition Dermatology Life Quality Index (DLQI) had been used in some of the clinical trials. However, the company stated that it had received advice that these measures were not appropriate for capturing the quality of life of people with EPP."* Response: The responsiveness of generic questionnaires such as the SF-36 and the DLQI on treatment effects have not been scientifically assessed in EPP and are therefore not suitable. We reject these questionnaires as tools to measure quality of life in EPP patients since they have not been validated for EPP. Biolcati et al. have developed a psychometrically validated EPP-QoL questionnaire with the support of an independent expert commercial provider (Oxford Outcomes). This EPP-QoL questionnaire is described as appropriate by patients and it is significantly superior to the generic SF-36 and DLQI questionnaires. Moreover, the latter was validated for dermatological conditions. EPP is not a dermatological condition, despite its cutaneous manifestations, and features completely different characteristics that need to be taken into consideration when measuring quality of life in EPP patients. EMA's EPAR report also notes the non-specific nature of the DLQI in EPP: "The Dermatology Life Quality	Comment noted. See sections 4.10 and 4.11 of the FED. Comment noted. See sections 4.10 and 4.11 of the FED.

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	Index (DLQI) was employed. This is a questionnaire not specific for EPP patients but widely used in dermatology for QoL assessment (e.g. in vitiligo, psoriasis, and atopic dermatitis) (page 901)." Here, it is important to refer once more to Hamming & De Vries who recommend that patients need to evaluate a treatment rather than just measuring health status as in these generic questionnaires. Not doing so, might result in misleading and inaccurate results such as when the DLQI is applied to EPP. Along the same lines EURORDIS, the European alliance of rare disease patient organisations, in its concept paper from the 23rd Workshop of the EURORDIS Round Table of Companies comment on the relevance of individual patient input: "Patient-Reported Outcomes are one way of obtaining such results. Those are measurements based on data provided by patients (self-report or interview) regarding their health condition without amendment or interpretation of the patient's response by a clinician or anyone else." And finally, EMA themselves have recommended that individual case descriptions be used as evidence: "Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse (page 102 in the EPAR report)." Section 4.9(b): *"The committee further noted that the company had developed a condition-specific quality-of-life questionnaire. Furthermore, the EPP-QoL had been modified while the trials were ongoing and data were being collected, and some questions were removed."* Response: First, the statement "the company had developed a condition-specific quality-of-life questionnaire" is inexact: The EPP-QoL was not developed by the company alone but in collaboration with the expert clinicians who authored the Biolcati et al. paper and who used patient input to appropriately formulate the questions. Second, the modification of the questionnaire "while data were being collected" is not relevant because as demonstrated by Biolcati et al. the removal of the questions from the first version of the EPP-QoL questionnaire did not affect the results of its final version: "During subsequent psychometric validation by Oxford Outcomes (Oxford, U.K.), a further three questions were removed (No. 3, 12 and 16). The scores were corrected for missing values by multiplying the sum of the answers by the factor: total possible answers/number of answers." Third, we want to reiterate the fact that the committee should have taken into consideration the inherent challenges of studying such an ultra-rare disease as EPP, a condition calling for increased regulatory adaptability and nimbleness. At the outset of the clinical trials very little was known about this condition and there were near to no extensive scientific observational studies of patient behaviours and disease impact. We as EPP and porphyria patient community, advocates and clinicians learned about the disease as we went through the trials and initial assumptions had to be amended during the process. It would have been inappropriate not to amend such assumptions as we learned more about the disease, e.g., by not removing	Comment noted. See section 4.10 of the FED.

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	inadequate questions from the evolving EPP-QoL questionnaire. This approach is also captured in the EPAR report as a normal element of the validation process: "The Applicant got the EPP-QoL revised by a CRO. The CRO were not able to fully validate the questionnaire but did review the scoring algorithm. Changes were suggested to the original EPP-QoL (e.g. omission of questions) (page 641)." While the CRO was not able to "fully validate" the questionnaire, we regard a "semi-validation" far superior to a "non-validation" like for the SF-36 and DLQI with regards to EPP. Again, the generic SF-36 and DLQI questionnaires should not be applied to EPP and the latter was validated for dermatological conditions and EPP, despite its cutaneous manifestations, is not a dermatological condition. Section 4.9(b): *"The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that people with the condition and their clinicians report as important. It also concluded that, without appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture any treatment benefits with afamelanotide."* Response: We strongly disagree with this statement: In our experience, the EPP-QoL was the only questionnaire that patients ever considered adequate to capture the symptoms and limitations of their disease. The National Reference Centre for Porphyria in Zurich, Switzerland, led by Prof Dr Elisabeth Minder has a substantial amount of data on this, in addition to those used in the Biolcati et al. paper. Full evaluation and publication of the data is pending but the evidence and patient testimonies clearly point to the EPP-QoL being significantly more appropriate than the DLQI. Moreover, we want to make the committee aware of the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which have been adopted by the EMA: "If quality of life is measured, it should always be assessed using scales validated for the particular indication being treated. It is recognised that sometimes there are too few patients for validation exercises as well as separate treatment evaluation." Unfortunately, the committee is not sufficiently taking into consideration a fact that is otherwise accepted by other relevant authorities: EPP is an ultra-rare condition with very low numbers of patients, and this disease and any treatment to address it cannot be adequately measured with generic tools. A disease-specific approach taking into account patient input has to be considered even if its full validation might not be feasible. Not doing so is a discrimination against EPP patients which we find extremely concerning. Other European EPP patient communities have not experienced this discrimination and have access to afamelanotide because their authorities recognised the uniqueness of their condition and applied adequate assessment methods. Section 4.11:"The committee considered the validity of the EPP-QoL to be highly uncertain (see section 4.9)	Comments noted. See sections 4.23 of the FED for a summary of the committee's considerations. Comments noted. See sections

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	and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty." Response: See our comments to section 4.9 Sections 4.3, 4.20: 4.3: "*The committee concluded that EPP can have a far reaching impact on the lives of patients and their families, resulting in anxiety, social isolation and very poor quality of life."* 4.20: "*The committee acknowledged that EPP, although not life threatening, can cause extreme pain, be very debilitating and have far reaching consequences on living a normal life. It was aware that even small increases in time spent under light could significantly improve people's lives. It noted that afamelanotide is the only treatment for preventing phototoxicity in EPP for which efficacy has been shown."* Response: We agree with the committee's assessment of the severe impact of EPP on patient lives and that afamelanotide is the only treatment which has shown efficacy in preventing phototoxicity in EPP. We want to add that afamelanotide also decreases the severity of phototoxic reactions and the duration of recovery after a phototoxic reaction (see also table on pages 74-75 in the EPAR report), two aspects to which little attention has been given by the committee. These two aspects are however of utmost relevance to patients who have or have had experience with the afamelanotide treatment as they are invariably reported to contribute significantly to the value of the treatment. These aspects have to be taken into consideration in the benefit assessment of afamelanotide in EPP and the related cost-effectiveness estimates. In addition and as a conclusion, we want to point out the contradiction between the statement in section 4.20 that "even small increases in time spent under light could significantly improve people's lives" and the committee's negative recommendation against afamelanotide for treating EPP. We are disconcerted about this contradiction and concerned about the negative recommendation despite all the evidence, patient testimonies and expert clinician input about afamelanotide effectively addressing patient needs and enabling them to not only gain a "small increase in time spent under light", which would already "significantly improve people's lives", but in reality to dramatically increase the time they can spend under light. We urge the committee to take our concerns seriously and to revisit their recommendation by applying appraisal measures in line with the peculiarities of EPP and with the considerable evidence presented.	4.23 of the FED for a summary of the committee's considerations. Comments noted. See sections 4.23 of the FED for a summary of the committee's considerations.
British Association of Dermatologists	Has all of the relevant evidence been taken into account? The expert and patient testimony has a prominent role in the evaluation of this treatment. That testimony has been taken into account in terms of the panel's response as human beings to the physicians and patients, but not for the evaluation of cost effectiveness. We acknowledge that this is difficult, and realise it may be challenging to do technically. However, we feel that if one did/could quantify "testimony" or "non-clinical trial	Comment noted. See section 4.9 of the FED.

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	data" (since the testimony shows such a dramatically greater efficacy than the trial data), it would result in a cost/QALY that would be fundable by NICE. We also think that part of the problem is that the trials picked up some of the efficacy but not all of it, which has led to the high cost/QALY. We note that patient and physician testimony played a significant role in being considered along with the trial data, in decisions concerning the licensing of this drug. We are aware that the situation with considerations of funding may be different from those faced by a licensing body but wonder if the expert team at NICE can think of a way of factoring this in. It is perhaps not surprising that the clinical trials have picked up a therapeutic effect, but not the full dramatic therapeutic effect, which was reported by patients and their physicians, to the NICE committee. The obstacles in conducting these trials were huge, both because of the challenges of dealing with a rare disease, and the difficulties regarding the measures and metrics used as endpoints. A further major challenge that was not discussed at the NICE meeting is the influence that seasonality of EPP has on its impact on quality of life and clinical scoring within clinical trials. As trials plan a springtime start (before patients face their major sunlight challenges, and so that patients are treated across the summer months) patients enter the trials with a low baseline clinical score and low impact on QoL as their condition is less severe at that time, with a seasonal worsening of scores during the trial as they go into the summer. Although the trials are randomised and controlled, this seasonal variation in severity is likely to undermine the full assessment of efficacy. There is also further evidence relevant to the DLQI to take into account. At the meeting there was much discussion, and questioning of a clinical expert, as to the potential reasons for the difference between the DLQI findings in the Holme et al. Br J Dermatol 2006 study (high DLQI score) and the EPP clinical trial in the New Engl J Med 2015 (lower baseline score). The clinical expert has examined the Holme paper subsequently and found an important aspect of the methodology was missing from the paper; she has personally contacted the paper's senior author who had also noted the omission, and provided the information that the DLQI was collected (by the junior researcher on personally visiting the patients) over the spring and summer months, i.e. predominantly when the patients would be most affected. This contrasts with the EPP clinical trials, where the treatment was aimed to start before the patients developed seasonal worsening.	

Commentator	Comment	Response
British Association of Dermatologists	Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence? Please see the response above.	Comment noted
British Association of Dermatologists	Are the provisional recommendations sound and a suitable basis for guidance to NHS England? We think the provisional recommendation is the wrong decision for patients with EPP. It is a deeply frustrating one and a deeply frustrating situation, for the patients, and physicians. If NICE could find a way of including/quantifying testimony from patients and physicians in the cost effectiveness calculation in some way, and potentially of quantifying the impact of the many unique confounding factors affecting assessment of this disorder, this would be invaluable. If the funding cannot be made available in the 'classical' way, we request that consideration should be given to creating a 'managed access scheme' or similar. People with EPP could be treated during an agreed assessment period (e.g. at least 2 consecutive years) for further data collection. This could potentially be done in specialised centres in Manchester (Salford Royal) and London (Guy's & St Thomas') which would also aim to help people with EPP alter their behaviour – "unlearning" a lifetime of avoiding the outdoors due to the severe pain endured), one of the factors that has probably contributed to the mismatch between the trial data and the patient testimony. The further data collection would focus on the lessons learned from the trials in order to collect information that more fully captures therapeutic effects by taking into account the following considerations: • additional seasonality consideration makes it challenging to capture the full benefit of treatment using generic assessment tools, especially combined with the significant others that were discussed at the meeting, including the need for a specific assessment tool for this complex skin/metabolic/apprehension-avoidance condition that appropriately encompasses the pivotal impact of sunlight • small differences in ability to tolerate sunlight exposure making major differences to patients • understandable hesitancy in sunlight exposure during limited duration trials due to learned behaviour following experience of earlier severe pain attacks, and time taken to adapt.	Comment noted. See section 4.22 of the FED.

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British Association of Dermatologists	Additional comments: There are issues around the assessment of orphan/rare diseases by standard scoring and costing models and perhaps these have contributed to the problem. Is there more scope to factor in a multi-dimensional assessment of such conditions, where it was understood that they may not always fit standard models? We are aware that the measure used is cost effectiveness per patient. Nevertheless, we would like to make the obvious point that EPP is a rare condition, so that the total cost of treating all the EPP patients in the UK with afamelanotide would be relatively low.	Comment noted. The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. See section 4.23 for a summary of the committee's considerations.

Comments received from members of the public

Individual number	Comment	Response
1	I write to you on behalf of all patients with the ultra-rare light intolerance erythropoietic protoporphyria (EPP) and particularly of those in the UK, recently affected by a disappointing recommendation by NICE. As I am in the fortunate position to live in Switzerland, I have access to the afamelanotide (Scenesse®) treatment since 2012 and was chosen as a patient representative for EPP during the approval process of afamelanotide at the EMA. At the last World Orphan Drug Congress in November in Barcelona, you vividly explained that the NICE appraisal process for Highly Specialised Technologies takes into account the specific limitations and challenges of every individual rare condition. Reading through the consultation documents published by NICE on December 20th, however, it became evident to me and the other members of the recently built Working Group of EPP Patients with Background in Science and Medicine, that the uniqueness of EPP has not been adequately taken into account during the appraisal of afamelanotide at NICE and that the real benefits of the therapy have not been recognised: In EPP, exposure to even a few minutes of sunlight and strong artificial light sources causes massively painful phototoxic reactions and severe burns in the vessels of the exposed skin, from childhood on. With afamelanotide EPP patients can significantly increase their exposure to light and experience less phototoxic reactions and, when developing them, these are of less severe nature: The treatment enables them to significantly improve their physical and mental health, and they become more integrated into society. In the NICE appraisal documents, however, the Evidence Review Group expresses uncertainty about the true extent of the benefit of the afamelanotide treatment in EPP, commenting that patients and specialised clinicians report hours of pain free sun exposure under therapy, while in the trials only minutes of additional	Thank you for your comments. The committee has fully considered all the evidence, including testimonies received. The committee acknowledged the burden of EPP (see section 4.1, 4.2, 4.21 and 4.23) and concluded that afamelanotide did offer a clinical benefit, but the size of benefit remained uncertain (see sections 4.8 and 4.9). The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of analyses in its decision-making. The committee considered that, in both the company's base case and the

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	sunlight exposure could be measured as compared to the placebo control group. I now would like to make you aware of the important aspect that the trials were conducted under quotidian conditions. This means that the measured sun exposure times were limited not only by the onset of pain, but also because of working hours and other factors like rainy weather, during which trial participants were not exposed to sunlight. The trial outcomes are expressed in mean daily values per patient, i.e. the sum of the exposure times to sunlight divided through all days without pain during the study period, including for example also the rainy days. Such a standardisation obviously cannot capture the full extent of the therapy's benefit. On the other hand, in their testimonies patients report of individual days during which they could be outside in sunlight for several hours. But this was only possible because on those days they did not have to work, did not have other duties indoors or the weather was not rainy. For the patients, being able to manage the few minutes they have to be outside to go to work without having to worry about sunlight is already a significant benefit. However, the true extent of the effect is much bigger as illustrated in the patient testimonies: Hours of sunlight exposure become possible under treatment. The described effect is comprehensible and also not unique to EPP: A friend of mine has severe migraine, and having found an effective medicine that she can use when an attack occurs is a major reduction in disease burden for her entire daily life, 24 hours a day, 7 days a week, although the attack itself usually only lasts for 48-72 hours. For a migraine medicine, a mean annual reduction in headache time would underestimate the true benefit of the treatment. Likewise, the efficacy of afamelanotide in preventing the occurrence and severity of phototoxic reactions in EPP is significantly underestimated when averaged out over the total duration of a clinical trial. EPP is an ultra-rare condition associated with known limitations in measuring the efficacy and benefit of any therapeutic intervention, like the considerable disease heterogeneity, the extreme rarity, and the lifelong conditioned behaviour which leads us to avoid light and sunshine at any cost in order to prevent having to feel the debilitating pain of our disease. We should not be denied access to the only treatment for our condition because of limitations in demonstrating its effect by conventional study designs and we are determinedly committed to making our voices heard loud and clear about our right to lead a dignified existence thanks to afamelanotide. To this end, we founded an international working group of EPP patients with a professional background in science and medicine. Currently, we help patients in all countries understand the scientific documents in order to be well-prepared for their involvement in the national regulatory and HTA processes, and with our support patients in the Netherlands, Germany, Italy, Austria, Switzerland and the US have already been able to contribute to making the afamelanotide treatment available through their respective national health systems and/or their medical insurance programs	ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources (section 4.19, 4.20 and 4.21). The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

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	I hope that I could raise your awareness about the important fact that the standardised trial outcomes should not be confused with the real benefit of the afamelanotide treatment in EPP: We severely suffer from light deprivation and the intense and excruciatingly painful reactions caused by a few minutes of light exposure, and no other effective therapy is available for our condition, and the benefit of afamelanotide is experienced by patients, including myself, as life changing. I urge you to please support British EPP patients, end their inhumane suffering and light deprivation, and make the normal life we are able to have thanks to the afamelanotide treatment possible for them, too.	
2	Has all of the relevant evidence been taken into account? Yes; Due account has also been given of patient testimony, in addition to published clinical trial data. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence? Yes, though it is noted that the company (Clinuvel) disagrees with some aspects of the assessment and modelling. Are the provisional recommendations sound and a suitable basis for guidance to NHS England? Given current financial constraints and pressure on NHS funding, the recommendations appear to be sound and fair I do not have anything further to add as the committee's assessment is extremely comprehensive and detailed.	Comments noted.
3	What can I say about EPP? Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to switch on the TV or look at your phone because every time you do you feel like you are on fire. Imagine not being able to do your job because the office lights cause you pain. That is my day, every day, not just in the summer, but even in winter. Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. I took part in a clinical trial for afamelanotide. My life changed. I went out of the house in shorts and T Shirt, I sat in the sun, I had the best year of my life. I went from suffering to enjoyment in a couple of weeks! I could spend hours out in the sun without pain for the first time in my life.	**To comments 3 to 35:** Thank you for your comments. The committee has fully considered all the evidence, including testimonies received. The committee acknowledged the burden of EPP (see section 4.1, 4.2, 4.21 and 4.23) and concluded that afamelanotide did offer a clinical benefit, but the size of benefit remained uncertain (see sections 4.8 and 4.9). The committee considered that it had adopted a wide view in considering the evidence base and factored in a range of

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	Now I'm back to hiding, avoiding things, I can't even take my children to school without wearing hat, coat and gloves. This treatment is life changing. I am psychologically damaged by this condition. I have suicidal thoughts because of the pain, and now my Children who are 3 and 6 are being damaged by this condition. Even though they don't have EPP they are scared to go out in the sun because it hurts Daddy. They should not be suffering just because I am. I am rapidly heading towards having to give up work due to EPP. Incandescent lightbulbs are no longer available to buy in the UK. Energy efficient bulbs, LED bulbs, Flourescent tubes and halogen bulbs all give off light in the spectrum that affects those of us with EPP. This means that wherever I go I am in pain, I struggle to use a laptop, a mobile phone, to watch TV all because of EPP. I sit at home some time, with the curtains closed, the lights off, the TV off, not even able to send a text message because the screen of my phone burns me. If EPP stops me working then the cost will be far greater than the cost of this drug. This is a pain that no pain killer can touch, a pain that no sun cream can prevent, a pain that leaves me permanently exhausted, but I carry on, because I have to carry on, for the sake of my sanity, for the sake of my marriage, and most of all for the sake of my children. I am bullied every day, I am laughed at and called names because I have to cover up. Can you try to picture driving a car in summer, wearing a coat, a hat and gloves. That is what I have to do, that is what I did to get here today. I have to ask people to turn lights off for me, to close curtains and blinds. Some days I will be in extreme pain but show no outward signs, no rash, no swelling, no tan. There is nothing wrong with me? I'm making it up? I wish I was. This drug is life changing, not just for me, not just for my family, not just for my employer but for everyone affected by EPP. If I had cancer you would give me Chemo. If I was addicted to heroin you would give me methadone. If I had a bad back you would give me pain killers. I have EPP. What do you give me?	analyses in its decision-making. The committee considered that, in both the company's base case and the ERG's exploratory analyses, the ICERs were substantially above the range normally considered an acceptable use of NHS resources (section 4.19, 4.20 and 4.21). The committee was therefore unable to recommend afamelanotide for use in the NHS in England.

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	You have the power to stop this pain, to stop this hurt and to stop this mental torture. The power to give me a life.	
4	I have the misfortune to have been born with EPP. A rare genetic blood condition. This has and still does affect my whole life. I am laughed at, even by medical practioners, also with comments such as, “aren’t you hot dressed like that” when covered from head to toe with brilliant sunlight shining. Yes I am hot, but much better than suffering the excruciating pain when my skin is exposed to sunlight, indoor outdoor lights. I have had my hands scrubbed with a scrubbing brush by a dinner lady at the junior school I attended, because she wouldn’t believe the discolourisation on my hands was not dirt. If you can imagine the pain I was already in before her attack on me hot coals under my skin then add what she did. Excruciating does not come near to describing it. To feel as though your blood is literally boiling day and night for days and weeks after a few minutes exposure to light is torture. To then have to be confined to a dark room and a few seconds at a time of very slight relief when something soft and cool is applied. When as a child we were given Calomine Lotion to apply huh, a few seconds of relief followed by a magnified excruciating pain as the lotion quickly dried on my skin. Nothing I have ever tried has helped with the pain, no painkillers, no sunscreen. The only thing so far has been to wear protective clothing, hats, long sleeves, trousers, socks gloves shoes or boots. Pile the clothes on while others strip theirs off. The only time I can feel slightly normal is during the winter months when others cover up because of the cold, the giveaway that I am not normal is my hats and face coverings. I am so isolated and depressed because of EPP. Even family members do not fully understand what I go through, “come outside its cloudy now”, cloudy it may be but the sun’s rays still find their target, me. Visiting people is out of the question as they have no tinting on their windows so they do not understand why I would keep my coat, gloves, and hat on when in their houses. For many years I tried to be normal but I always cried alone at night keeping my pain to myself. Looking as though nothing is wrong with you doesn’t help as no one can imagine or believe how much pain I go through each and every day of my life. I have heard of the wonders of the implant, how those lucky enough to have taken part in the trials have had such fantastic times in the sunshine. This I can only dream of and long for.	

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	To be able to go out in the sunshine, to be able to go out without having to get dressed up as if going on an arctic adventure. Must I die without this dream becoming a reality for me and many many others suffering the same fate. I take vit D tablets daily as prescribed by my EPP specialist, this has only been for the last 5/6 years, as before I saw no one who could or would help with my EPP, I need to take a large amount as I protect myself from the sun to such an extent. Being anaemic as my body cannot absorb iron because of EPP, means I am tired most of the time as supplements would endanger me. My vit D levels have been so low an EPP specialist was amazed that I had not had any fits. Before the law was changed in the UK on window tinting I was able to go out and about driving all over the place as the tinting applied to the windows helped enormously plus my usual covering up. I even passed my advanced driving tests. I can no longer do that as having to have 75% of light coming into the drivers windows has put paid to that as I cannot go out so much because of the pain it causes.	

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5	Before you decide not to go ahead with this drug for people who suffer from EPP I would like to tell you about my son who has EPP and has a daily struggle with it. My son is called James and has suffered all his life with EPP. He is the only family member with it. He is now 14 years old and still suffers from it. The thought of him receiving the drug at 18 keeps him going at times. He gets bullied at school through having EPP and has had phone calls from other lads his age threatening to burn him with torches and at the end of the day he just wants to be "normal". Here's a question for you, Have you ever seen your child in so much pain and all you can do is watch them suffer as a hug burns them more. My son burns inside out and the pain is written all over his face. The only thing that soothes his pain is by applying cold water and this might give him seconds of relief. He takes paracetamol and ibuprofen together with an antihistamine and this doesn't ease his pain. He burns for days at a time. When his hands are on fire I have to feed him, help toilet and wash him. When his feet burn I have to carry him as they are too painful to walk. When his lips are on fire he can't eat anything hot as this makes his lips burn even more. He has lived off ice pops and ice cream for days at a time. James's lips split very deep leaving them scarred. His face swells up which adds to the discomfort he endures. He is always vitamin D deficit and takes vitamin D supplements every day. His body doesn't use iron properly so is always anaemic but cannot have iron supplements. He has become calcium deficit due to the vitamin D deficiency which leaves him having palpitations, bad stomach pains, bad nausea, dizziness and nearly being admitted to hospital. He has to be covered up constantly even in winter with protective clothing which consists of a hat, long sleeves tops and jackets, long legged pants, gloves and a face cover. He has people staring at him and talking about him. He has been accused of trying to rob the post office and asked which bank is he going to rob. He has been classed as a thug type with all his protection on. This upsets him greatly. I have to encourage him to go outside at times with his friends. He refuses to go on school trips abroad just in case he has a reaction as he doesn't want to spoil thing for the other school children. I have even signed his forms and he hasn't handed them in. He has started light therapy to try and build up his pigmentation and help him not have as many reactions. This causes him to have reactions at the beginning of the treatment. He has 15-18 sessions of this and it goes over a period of 5-6 weeks. James has blood test every 3 months to keep a check on his vitamin D levels. This affects our family greatly as we have to go on days out on cloudier days. We don't go to the beach in the summer with our two younger girls who don't have EPP as it gets too much for James in the heat. James is constantly tired due to the iron and has to have plenty of resting and cooling down times if we do go to an event in summer and have to plan for indoor activities as well. If we're going swimming James has to wear a full swimming suit which he wears if we get the paddling	

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	pool out and he goes in the pool in an evening or when the sun isn't at its hottest. We have never taken James abroad as I wouldn't want him to suffer whilst over there and he would feel guilty if he spoilt our holiday (which we would never make him feel like this). James is a polite young man who tries his best at everything. He pushes himself to his limits and most of the time ends up suffering as he wants to be "normal" with his friends. James also suffers from headaches at school due to the whiteboards and computer screens and lighting. I have bought James glasses from the opticians which have a slight tint on them to try and stop this occurring. In sport's at school he has to do games outside and he has to wear his p.e kit which is a short sleeve t-shirt and he wears a long sleeved under armour underneath it and jog pants with his hat and gloves and face cover as well. Some days he can only take part for 15 minutes and other days his teachers won't let him take part as it's too hot. If James could have the drug to give him a "normal" life now I would let him as I feel he's had a rough life up to now and if it stopped the bullies calling him names and abusive behaviour towards him he would have my 100% backing. I have had to fight for every little bit of help for James, even had a two year fight with the GP to get him referred to the hospital at 4 years old. I had to be filmed for a t.v show to get help from the council to get my windows tinted so James could be safe in his own home. As working parents and a working family we pay our taxes and support people who need medication through more common conditions and through drug rehabilitation. I feel like throughout James whole life there has been a fight for everything we need for him. I for one will put up a new fight for the implant to be approved and I know that there would be many more people.	
6	Patients with EPP suffer extreme pain when exposed to the sun. I have seen first-hand what a debilitating illness it is as my brother-in-law is a sufferer. He has missed a number of family events due to not being able to be outside during the summer or if he attempts to join us he often suffers the painful after effects for days afterwards. By denying EPP sufferers access to the drugs which decrease their painful symptoms I feel that you would be discriminating against them, as this illness prevents them from taking a full part in family life, which impacts also on their families, and also prevents them from applying for certain jobs that require them to spend any time outside. Through providing these drugs people's quality of life would be immensely improved as well as taking away their pain and suffering.	
7	NICE are asked to consider the massive impact on everyday life of people suffering with EPP. Extreme pain from exposure	

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	to sunlight, results in total curtailment of participation in outdoor activities. The psychological effect on children not being able to play with friends should also not be underestimated, and long term impact on self-confidence is also significant. This treatment is proven to make a massive difference to everyday life for EPP patients and NICE are urged to given sympathetic consideration to its prescription for all those affected by EPP.	
8	To be honest I wish to tell my story. I was born with EPP and have known no different. Since as far back as I can remember EPP has had an effect on my life, it has destroyed my childhood, where other children are able to play outside I had the choice of being socially included and enduring agonising pain during the whole of the next 48 hours or being a social outcast! I chose the outcast route as it was less physically painful. As I grew up I noticed people backing away from me as I couldn't join in normal social activities. It is hateful and there have been times when I pleaded with the devil, selling my soul to take this misery away. EPP still has a massive impact on my life and will do until I die unless there is a reprise from the daily misery of this condition. I would not wish this condition on my worst enemy. It also has an impact on my ability to contribute to society in a meaningful way. I can't stay outside too long owing to the reaction I experience, which is a tingle, the precursor to the burn that is inevitable which keeps increasing for at least 6-8 hours where my skin is on fire, I self-medicate to try and bring relief but to no avail. The worst part is knowing that while I feel this pain I can't avoid light the very next day which brings on more burning to add to the burn I already feel. The cycle goes on! All I want is after 47 years of life I can have some quality of life before my life is over. As I type this with one extended finger I am thinking about the pain of the light from my tablet screen and how my finger will burn later. I ask you to consider the use any drug to give others and myself a chance at life without guaranteed pain. I have had EPP from as long as I can remember. I and now 51 years of age, but I remember having extreme pain after exposure to light, even as a small child. The pain is really indescribable to anyone who doesn't suffer with EPP. No one really understands how this condition affects you, unless you are of course a sufferer yourself. It is like your skin burning all the time, as if you've burnt yourself with hot oil or a sticky substance, where it penetrates under the skin. Nothing helps, no painkillers, no creams, nothing at all. You have to hide yourself away in a cool dark room until the pain subsides, which can take days. You cannot sleep at all as the pain is so severe, burning, burning all the time. You cannot bear anything to touch the skin as this sets another pain to add to the burning and can be a like a hot knife twisting into the skin. To try to cool the skin you have to put on cold water, but this only gives relief for about 30 seconds, but those 30 seconds are bliss. After that you return to the burning pain.	

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	The lack of sleep and the pain changes you as a person. You don't want to be bothered with people. This affects the whole family/s,they want to help and can't. You're short and grumpy with them as you are dealing with this severe pain and then to top that, the lack of sleep. You start to feel quite depressed and very low. You think about how you get escape the pain. You cannot share this experience as it is too difficult for anyone who doesn't have EPP to understand. Despair usually sets in at your lowest point and you get thoughts of how best to get out of the pain. This pain sucks all the energy and life out of you, so much so, there has been times I have for a short time, wanted to end it. We were born with this condition, to which there is no cure, but we have a light, excuse the pun, at the end of the tunnel and that is Afamelanotide. This would drastically change our lives. We could join in with family activities, walk the kids to school, play with them in the park, go to the shops, and any of the normal day to day things that most people take for granted. Instead of hiding away, avoiding the sun, staying in the shade and shadow hopping. This hermit lifestyle has its own toll on your mental health, as when everyone is enjoying the sunshine, you're on the side-lines watching and not being able to join in. Then there's being fully clothed in temperatures that everyone around you are in shorts and vest tops. You're having to wear longs sleeves, trousers, trainers, gloves and a hat, so you're baking hot and cannot get any relief from the heat and that's besides the ignorant stares and comments from people. This just gives you an idea of what it's like living with EPP and what life would be like with the help of Afamelanotide.	
9	I am married to an EPP sufferer and we have a son who also has EPP. I can confirm the massive, and detrimental, impact that EPP has on the life of the sufferer and all other members of their family. I note that your papers refer to the patient expert who states what a huge effect this treatment has on the Quality of Life, but that this is not effectively measured by the clinical experts. I would suggest that this difference is due to nature of the clinical measurements being defective. Historically all disease has been measured by how quickly it kills the patient. EPP is a chronic disease rather than a critical one, therefore the measurements need to change. My wife can be debilitated by EPP with swollen hands, feet, face, etc to the point where she cannot move her hands, or walk and is unrecognisable, with unbearable pain that no analgesic can control. There have been times when she has considered suicide just to make it stop. At the moment our Son, who is 30, seems to respond slightly differently in that he constantly feels exhausted, the more exposure to the sun, the more exhausted he feels. As he is married and hopes to have a family soon, this could have a major impact in how he is able to support his family in the long term. When younger he also suffered swollen face and limbs, but since becoming a young adult the exhaustion has become the prime symptom.	

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	In terms of cost, if there are 394 people diagnosed with EPP and the annual cost is £48,000 per patient then the total cost is less than £20M per year. At the moment the NHS spends £14Billion per year treating Type 2 Diabetes which is, almost totally, self-inflicted by poor diet and lifestyle. These 4 million people are able to continue with their appalling habits because the NHS keeps them alive with what has become extremely expensive medical intervention. If the NHS refused to treat Lifestyle Type 2 Diabetes then these people would have to choose between changing their diet and lifestyle or dying. EPP sufferers have no choice, they are born with this condition, and will die with it. Your clinical expert has stated that there is currently no effective treatment for this disease. This is a very effective treatment. This is dramatically innovative, and the most positive thing that I have seen in my 26 years working with EPP patients. It would be a complete travesty of natural justice for myself, my wife and our son, to continue struggling to work and, therefore, pay tax which is used by the NHS to treat people with Type 2 diabetes while we cannot get the only treatment for EPP that will actually work. By treating EPP it will enable all 3 of us to become more reliably productive and actually pay more tax into the system which will recover at least part of the cost of treatment. By treating Type 2 Diabetes all you achieve is to encourage those people to continue with their lousy lifestyle, have ever more health problems and cost the NHS ever more money. Quite simply, there is no justice in refusing to fund Afamelanotide.	
10	My partner has an EPP diagnosis (..). He was diagnosed officially at the age of 35 and prior to this new from an early age that he was allergic to the sun. This has severely impacted on his life and also us as a family. We have never been able to have normal holidays in the sun or days at the beach due to the reactions he may have after just 10 minutes. If my children have been to the beach or park with their dad it has been in the evenings when all other children are indoors or in bed. As soon as the spring is approaching this causes us all a level of anxiety due to the up and coming hot weather. If we are invited to a barbeque we cannot go until the late afternoon or any sooner then we have to stay inside when others are outdoors enjoying themselves.	

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	A day out or travelling to work consists of my partner wearing expensive tops, gloves and neckwear brought from the USA. He resembles a bank robber or a person who is up to no good and feels embarrassed that he looks so different, we are also concerned that he may be stopped by the police due to the levels he has to go to just for protection. When at work and in the building my partner is not safe from UV rays as he also can have reactions from the lights in the office. His job role requires his to visit service users and again travelling causes him reactions. If my partner should push himself trying to be normal for a very short time he becomes ill, irritable and has to go to bed which has impacted on us as a family when at home or on holiday. We have been excited at the thought of us being able to do normal day to day things with the new medication that has been approved. I do realise this is expensive; however this could dramatically improve life for my partner and allow him to not feel different.	
11	I am one of five children who have different fathers, out of the five I am the only one who has had to suffer the torment of living with epp all of my life. I want to give you some insight into my life and why I am upset that the drug Scennesee is still not being given to patients as a matter of right to improve mine and others quality of life. This condition which is very rare has impacted on my life since I was a baby, during the sixties I was always crying during the summer and no one knew why, they thought it was many things but they never suspected that it was the sunlight that led to my extreme pain which is not understood by those who do not have the condition. In later years I have made connections to others who have this same incredibly debilitating painful lonely condition and now have some sense of belonging to a group of likeminded people who understand why I look strange dressed in thick clothing to stop the sun getting onto my skin during the summer months. Going back to my childhood the GP advised that it was the London air which unsettled me, they advised I should move near to the seaside as this “works wonders for many ailments”, not in my case It did not. In fact it made it worse, my mum naively took me to the beach most days to play in the sand and enjoy the seawater as well as feeling the cooling breeze on my skin. For a person with epp, this was the worst thing ever, as a baby I could not explain what was wrong, and there are usually no outwards sign immediately to indicate there is a problem, however dependent on how long I was in the sun it led to scabs forming on my nose, and further mickey taking as I grew older. My mum only knew that I was always crying and she and the medical professionals could not do anything to stop this. Eventually as I got older it was explained that I was allergic to sunlight. From his point on then at least I could avoid the light, however this led to isolation from family and friends. I grew up on a council estate, our playground was the streets the parks	

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	and the seafront. I did go out to play but so many times I became ill and was then having to stay in for days on end. I missed school, my friends nicknamed me “vampire” during the summer months. As a child this is extremely hard to cope with, I remember one day lying in my darkened room and looked at my hands which were on fire from the inside out. The hands were swollen as was my face and knees, but all I could see was my hands and I asked god, “why is this only me who has to suffer this pain all the time, my mates don’t have to put up with this”. My thoughts at that time were if I cut my hand off, will the pain stop? I was aged around 12-13 years and really wanted to do this. I told my mum who then made sure she kept a close eye on me to avoid such drastic measures. I was immature and naïve and yes it is a silly idea, but you know what even today at 53 at times I want to remove the pain, and feel like cutting them off again but I cannot. Another memory from a childhood with epp involves a games teacher at my all boys’ school it was the summer of 1976 and a heatwave was upon us. My mum wrote a letter to the games teacher Mr Kay who once given my letter asking to be excused from the games on the field called upon my peers, which consisted of two year groups. He asked me to stand next to him while he read out my mum’s letter. His words have always stayed with me; boys gather round, Gentle has come up with the most feeble of excuses, he has written that he is allergic to sunlight (huge roars of laughter from my school year) Gentle believes that sun hurts him, but in fact without sunlight we would not be here (more laughter). Even writing these words takes me back to that awful moment of being ridiculed in front of so many, and it makes me very sad to know that this condition of epp us still not known enough about and there are many more who are still suffering If the drug is made available then further ridicule of others can be prevented. Into my adult years the hurt does not go away, I do not get burnt as badly as when I was a child but the pain is still the same when I am caught out in the sun, or if tricked because I think the cloud is thick and I may be protected, I have got caught so many times and been in pain for a few days having to miss time with my family and also missing my paid work which is an indoor office role as I cannot risk being outside for long periods of time. I will bullet point what epp stops me doing to stop this becoming a rambling email, however what I do recognise is that once I start putting words down It brings back to me how much I have had to miss out on during my 53 years of life: • Days at the beach / park with my children • Missing school sports day • My children becoming embarrassed when I am fully covered, as adults they understand the condition now, but as	

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	kids I was the “weird dad”. • Not taking them to theme parks in summer, always going in the winter months. The levels of anxiety when I planned days out and the sun was shining, I would be the only happy when it was thick cloud - Days out with friends to outdoor festivals - Having to endure being looked at constantly because I am wearing gloves jumper, long thick jeans to stop the light touching my skin. - Having to avoid areas where there are lights with UVA that hurts me. - I cover up while driving and have been questioned by police as to why I am wearing gloves and neck and face protector whilst driving. I now have to carry information leaflets to explain my condition from the BPA. - Summer holidays abroad, hardly ever - Holidays in the UK, yes but still got burnt so many times. - I studied for a university degree in my 40’s, my face often got burnt due to the rays emitting from the computer that I was constantly sat at writing assignments - I had to down a friends recent wedding invitation as they are marrying on a beach. - Summer 2016 at my brother’s wedding I had to be away from the main party under a tree as the wedding was held on lawns of a country house. - I now watch the summer holidays adverts on TV and it reminds me of the pain I have to prepare for again from March onwards. - While reading this to my partner today, I had not realised how much this has affected me, I started to cry when I recalled my childhood, it is probably as I have not been so open about this before. This took me by surprise, however it is a lot of trauma I have had to deal with for many years without support. - I was diagnosed in 1999, I found a magazine article that spoke of a child who could not bear sunlight, I took this information to my GP and an appointment was made to see Professor Hawk St Thomas’ Hospital London. Being able to name the condition has been life changing, and I will now talk more freely to my colleagues and friends of my very rare condition. My whole life including the forming of relationships has been affected due to me not being able to out as any normal person, I have to plan ahead constantly to avoid becoming burnt and in pain. I have always prayed for a miracle to happen, I was told as a child that allergies have seven year cycles, I kept on hoping that my 7 year miracle would happen, scenesee has been discussed and tested for a number of years, please consider the	

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	impact this has on my life and that of my fellow sufferers. We just get on with it, but my life has been impacted greatly by this and I need to enjoy my later years of life being able to enjoy sunshine as much as the next person. Please reconsider the application and bear in mind that it is not only the patients who suffer, there is a ripple effect which affects my family, friends, work and my overall well-being in the world.	
12	My brother has suffered EPP all his life he is now 53 yrs old. As his sister and many other siblings and family members already know the pain and suffering their family member is going through.... It's horrendous the pain I saw my brother was in. One memory of many is my brother is 5 yrs older than me he is a good brother but I remember him being in his room I went straight in and saw my grown up brother crying in pain his eyes were so swollen they were closed his hands and legs had cold flannel on as they were the only help he had.... he shouted at me to get out I was so upset to see him like that. Another memory is my brother went away for a weekend trying to do something normal be a teenager and we had an emergency call to collect him, he was sitting in a corner in absolute agony. Please tell me why can my brother and other suffers of epp have the drug that can help them and stop their suffering. Why are you letting young children and adults continue to suffer it almost sounds barbaric please allow this drug to be used. From only 1 sibling of many who want to help their family.	
13	How would I describe my pain? As rolling around naked in a field of stinging nettles.. can you imagine? All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain. When I learned about Afamelanotide and what difference it could make to my life, I cried. Not because I thought I would be able to lay on a beach but because I would be able to do the little things "normal" people take for granted. Taking my children to school, watch them participate in a sports event, hanging out the wash, take my dog out, teach my son how to ride his bike and most of all, not feel different to other people and not feeling like people are sniggering at me and talking behind my back. To be able to sleep a decent night. Not being up in terrible pain. Not knowing how to get any relief. And now I learn you may take this away from me.. I feel sad, depressed and angry. If you had to live with my pain for just 10	

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	minutes, this would not be up for discussion, this would be granted straight away. PLEASE consider our pleas. PLEASE change my life???	
14	I am the parent of a 16 year old son who has suffered the effects of EPP since he was 4. No family history we are aware of. Please consider the severe pain sufferers endure with minimal exposure to not just sun light but even some indoor lighting. The suffering during a bout is heart breaking. The mental pressure this brings is also a huge concern, he's had to be excluded from activities "normal" kids take for granted. As he grows he will be excluded from most social events, festivals, holidays with friends etc - possibly leading to a "reclusive" loner life. There is currently little to alleviate the pain and certainly nothing to help prevent the onset and therefore allow a little more exposure to light. I'm sure you will be aware EPP brings possible complications with liver function and we really believe all lives should be enjoyed while young. EPP is a disability, would visible signs make the decision different? No cure and this drug is proven to be a huge help for sufferers in other countries. I ask you to reconsider this decision, or at least keep the discussion open until the supplier price is reduced.	
15	In simple terms this drug would change my life. It would allow me to lead a normal life and to have a good quality of life. At the moment I live in fear. I am confined to my home and unable to carry out simple tasks that others take for granted but worst of all I cannot give my children everything they deserve. Unfortunately my 5 year old daughter also had epp and we are waiting to get my 1 year old son tested. I do not want them to have to feel the incredible amount of pain that I do and to feel trapped in their own home. I understand that the NHS is under immense stress but this drug really would change mine and my families lives. I have had this condition since birth and it will never improve or go away.	

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	Please approve this drug so that is available on the NHS and allow me to lead a life that many people take for granted. I do not want to live my life in pain and in the shadows any more.	
16	I am an EPP sufferer and was diagnosed with EPP at the age of 32 after a lifetime of crippling pain and mystery surrounding what was wrong with me. I suffer year-long and am largely unable to spend any time outside. My condition has affected my life in so many ways, including mental health, career choices, ability to travel and experience so many aspects of life, as my ability to be outside is so limited. However 'being outside' is a misleading way of referring to it.. I have been told to 'stay indoors' 'not sunbathe' etc by many doctors; what people miss is the fact that exposure to light is not a choice. Many days a year I am unable even to walk from house to car, car to workplace etc. It is not a case of avoiding the sun by staying off the beach, shade hopping etc, there are days when EPP renders the sufferer unable to function without an incredibly high level of support, and perform even the most basic of everyday tasks without as a result, being subject to the most crippling pain imaginable. I have a ten yr old who, unfortunately, has been affected significantly by my condition. I spent 7 years as a single mother with a limited support network locally. She has experienced many days indoors when she should be in the open air, not watching her mum hide inside and cower at the faintest hint of light. I had hope when I was diagnosed, hope that after a life in the darkness, finally something could be done to improve my (and my family's) quality of life. I had hope developments were being made and some day in the future, my life could become closer to normal. The idea that we have an effective treatment that is potentially being denied to people like me breaks my heart. Here lies an opportunity for people like us to function on a day to day level, work in the jobs we want to do - and need to be successful in, be the kind of parents our children need us to be, and basically have access to the sort of existence others take for granted every day. WE deserve this. Please take all these comments into account, don't just read them, LISTEN to them. Realise the importance and magnitude of what could seem like a throwaway decision regarding an extremely rare condition. There may not be many of us, but we deserve better - we deserve access to a life of freedom and opportunity.	
17	With regard to the decision by NICE not to include Scenesse for reimbursement by NHS England, I would like to add the following comments in the hope that NICE will review their decision. Our 16 year old son suffers from the rare genetic disease called Erythropoietic Protoporphyria (EPP), the past few years have been unbearably hard for all of us. When he has a reaction, the reaction is like a horrendous burning sensation under the skin - like have boiling water burning you on the inside. Once he has a reaction, it takes a few days staying inside before the symptoms start to subside. Once a reaction has occurred even a hot room can exasperate the symptoms. It has a cumulative effect, in so far as, once you've had a reaction, over the next few days, any sunlight will cause an even quicker,	

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	often immediate, reaction to occur. The burning is so bad that it is impossible to find any relief and impossible to sleep. The only way to avoid a reaction is to avoid going outside in the sun. This has a huge impact on our son's quality of life. Can you imagine your child not been able to go out in the sun? He can't go outside at lunchtime at school. In summer he has often been sent home from school and missed lessons because the classrooms have got too sunny and hot (glass offers no protection either). He can't go out with his friends after school or see them on a weekend or in the school holidays - unless they are inside. Family holidays are a logistical nightmare and camping is impossible. Hats and gloves offer only a short reprieve, allowing him to go out for an hour or so, as the sun reflects off the ground and hits the face. Water is particularly bad for reflecting sunlight. Furthermore, once he's had a reaction, hats and gloves are no help at all - the heat of the day means that the reaction is maintained and immediate. Getting into a building asap is essential or the reaction escalates. Stepping outside again is impossible until the reaction has had a few days to calm down. The first reaction usually occurs around April/beginning of May and he will then be susceptible to reactions until October - that's 6 months of the year. He desperately needs this drug to dramatically improve his quality of life and his well-being, especially as he reaches adulthood and independence, with university on the horizon. As it stands, he is effectively imprisoned in bricks and mortar every summer - for the whole of his life. Please, please, please, put yourself in his position and imagine what it would be like not to be able to step outside into the sun, to be confined to indoor spaces all summer, to not be able to sit in the front of the car (glass offers no protection from the sun for EPP suffers), to not be able to go for a walk or a bike ride, to not be able to sit outside at a cafe or pub, to not be able to go into town with your friends, to not be able to go and visit all the wonderful cities in Europe, to not be able to go on holiday with your friends, feel the warmth of the sun on your face .... please, please, please don't let my son be a prisoner forever. This is a very rare disease and there are only around 500 sufferers in the UK, even less in England, it seems such a small price to pay for such a massively enhancing and life-changing drug. It's not going to have a small improvement in quality of life, but an absolutely HUGE improvement in quality of life for people with EPP.	
18	I am a mother of a 53yr old who has suffered EPP since a baby.	

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	I have seen him go through so much pain and swelling. As a child he was told he was allergic to the sun but could come in a 7yr cycle which of it wasn't. One day I sent a letter to have him excused from games and not only was he ridiculed by his peers also his teacher thought it was a hilarious excuse to get off games. This has stayed with him the whole of his life. He is now 53yrs old and over the years he has prayed this treatment to be available in the UK. Pease give reconsideration to allow the treatment to be used here. Like any mother I'd like to see no more people have to suffer like I've seen my son suffer. This treatment is as important as any other illness. Why are these people not helped?	
19	Since last Summer I got a treatment with Scenesse at the University CHARITE in Berlin. The only thing I can say: "WOW" My Life changed 100 % !!! Decades of heavy pain in the Summer are now over. Now I can play with my grandchild's in the garden and at the seaside without any Problems !! In five Weeks I will get my first treatment with SCENESSE for this year. EPP is not just a smart sunburn, it produce heavy pain just a few minutes after the skin is exposed with sunlight. Greetings to Great Britain and good lick to you.	
20	It is so important to approve of Scenesse. It changes the lives of EPP patients. Why deny a treatment with no side effects but with an immense benefit? My review of life being a 24 year old German EPP patient Being in the light filled me with insecurity, fear, anger and most of all with immense pain for almost all of my life. From having the first symptoms being two years old till three years ago when I first was treated with Scenesse living life was more than just complicated or difficult. The most simple things or daily life activities always resulted in me being in exceptionally strong pain. No matter how long I stayed in the light, no matter how much of my skin I covered up. It always ended in me being in pain. A burning, itching, sizzling pain. Deep in my skin. Feeling immensely hot, although my skin was ice cold. Scratching myself bloody to relive the pain for just a short moment. Very sensitive to pressure, to more light, to cold things to warm things.. Sensitive to everything. I could not bear my family comforting me because that meant even more pain. And all of this this would go on for days - sometimes up to seven days long. And going outside would only extend the time being in pain. But you have to go out. You have to go to school. Or to work. Or to the doctor. Or go grocery shopping. That is very hard.	

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	Especially when others do not see the pain. People do not believe what they do not see. They belittle your invisible pain. You have to explain yourself over and over again. You are always being watched differently and I always heard stupid comments on why I am wearing long sleeved clothes and a hat and an umbrella and gloves and shades. As a child being invited to class mates' birthdays I would always say that I do not have time on the day of celebration because I would know that it would end in pain. So I missed out on a lot of activities and normal childhood experiences. Looking back on my childhood and being a teenager I remember that every activity involving me included special measures to keep me safe but in the end I would have to endure pain. Me having sleepless nights. Drifting in and out of sleep and nothing would lessen my pain. I had hard times paying attention in school or even attending school. I was 16 when I started to take painkillers - morphine. And I was not like I was not in pain anymore - I was too high for the pain to bother me. My body and mind were not connected anymore and so I did not care for the pain. And I got used to the dose. So I would take more and more than the prescribed tablet every six hours. And it did not mean that the pain would be over faster. But that I would drugged till pain was bearable. I was lucky to not be in an accident during those times. My mom always referred to me as her basement-child. That is where I would love to stay. In the dark and cold - far away from the light. I never dared to dream of it being different. Of me not being scared going outside. Of me not always being in pain. But it changed! It has been three years now, since I first have been to Zurich to be treated with Scenesse. It is such a simple procedure with such a huge impact on my life. I am able to go outside for hours - into the direct light without covering up and without being in pain. Sometimes I still experience pain after being outside. But those times are very rare and the most important thing is that the pain is not nearly as intense and not as long as before. It is just like a normal mild sunburn. My self-confidence has grown. I am not afraid to go outside anymore. I do not have to plan every single step. I generally think more positive. I am more open minded. I have more possibilities. I am able to take part in life like anybody else without a disease. I have not taken a single painkiller for the EPP symptoms in three years. I do not feel like an EPP patient anymore.	
21	My husband suffers from EPP. At times, it has left him in severe pain. His skin swells and is red, you can feel the heat coming off his body from a distance. It affects his mood. He can't sleep. Even the slightest light/water/touch of anything to	

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	his skin causes him severe pain. We have to sit in the room with lights/tv off as these will add to his already agonising pain. We can't go on family holidays unless it's grey out or it will cause him distress. Our two sons are missing quality time with their dad because when the weather is nice outside and we want to play out, he has to hide inside. He goes whole days in summer not leaving the house until evening when it's starting to get comfortable enough for him to go outside. Usually after bedtime for our children. When we've been for days out to farms etc he has to hide in shadows while wearing hat and coat and gloves. He has to avoid outside as much as possible. This has severely affected our relationship as well as with the children. They have got used to "daddy can't go out in the sun" "daddy burns in the sun" and will automatically assume he's not going anywhere with us. When we are in the car any time of the year he needs to wear gloves and coat to keep covered. He still hides his hands out of direct sun regardless of gloves in summer as it still burns thru. When he was taking part in the drug trial he was able to spend not just minutes outside but hours, in a t-shirt, with us as a family and didn't suffer. He was happier, healthier and was able to feel "normal" for that time. Now he is depressed, always in a low mood, lacks interest in doing anything and it is physically affecting him too. He is on medication for lack of vitamin d. He has been suffering with constant illnesses from a low immune system. Every year he starts to suffer earlier than the last and the reaction is worse. It is a debilitating illness. This drug is life changing. Not just for those who have EPP. Those of us who live with people with it are also suffering. Please let us have a normal family life. If you saw the look on a child's face when you tell them for the hundredth time that "no daddy isn't coming" your heart would break too. Like mine does when my sons want to play with their dad and he can't because he is either suffering now or will later. I see him force himself to get out to try and spend time with them and I see him suffer afterwards. I can't watch someone put themselves through that agony. Can you? Please give us our lives back.	
22	I have read all the documents pertaining to the application for Afamelanotide to be made available to treat Erythropoietic Protoporphyria (EPP) and attended the first Scope Workshop held by NICE in 2016 as a British Porphyria Association member and EPP sufferer. So, I am aware that I cannot offer new evidence with respect to the need for this treatment. I am asking, however, that the following be given consideration. I have EPP with severe intolerance to visible light which became active when I was 1 year old (diagnosis was at age 22). My life has been completely dictated by EPP with respect to education, career and life style. As a young child I experienced such extreme pain that, before the age of 12, I had decided that suicide was a viable option if the pain made life unbearable. I thought this was a smart decision. It was only as I got older I realised that this was not something that would be considered a normal way to live. As an adult I have had more control and autonomy and have made life choices around the constraints	

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	EPP imposes. I am dependent on prescription drugs and addicted to the pain relief drug codeine. I have two children. My decision to have a family was based on the genetic/hereditary evidence available at the time which I started my family which stated that the chance of passing on EPP, with symptoms, was highly unlikely. Unfortunately, this data was incorrect and research that took place after my children were born revealed that the chances of passing on the condition were much higher. I would not have had children if I had had this information. My daughter (now 20) has the EPP gene but does not currently have symptoms although these could still develop and she could pass EPP to her children, should she choose to have a family. My son has the EPP gene and developed symptoms when he was 8 years old. My son is now 17 and the last 9 years have been unbearable as he has an extremely low tolerance to a very wide range of visible light including a range of artificial light as well as natural light. My son failed at school as it was impossible to provide a safe environment for him. Eventually, we obtained an Education and Healthcare Plan to support him which has enabled him to attempt education at a sixth form college. This requires a support team which includes transport (a taxi) provided by the County, site personal changing areas of the college so my son can be safe while he studies, a one-to-one coach to enable him to catch up on work missed due to his health and access to a counsellor I have had to give up full time work and am his carer working part time around his needs. Last year I was on the verge of bankruptcy but my Father's death and a small inheritance has kept us afloat. My daughter, despite being symptom free, has had a life dictated by EPP and has had to act as a carer for both of us. My son has a proactive consultant who managed to make a red cell exchange treatment available for him. The aim to try and provide him with temporary relief from the terrible pain and stress of trying to avoid light. This procedure is, obviously, extremely expensive and needs a multidisciplinary team to facilitate it. The procedure works by removing red blood cells containing high levels of porphyrin and replacing them with donated red blood cells thus reducing reaction to visible light for a temporary period. Unfortunately, my son's veins cannot stand the procedure so it has only been successful 50% of the time. It has been extremely painful with his veins collapsing and permanent scarring from a femoral line. Additionally, he suffers from extreme fatigue and low blood pressure after the treatment with recovery time taking a week. Even so, throughout 2016 and the early part of 2017 he continued to attempt the treatment on a regular basis in the hopes that a successful exchange would give him respite from the terrible pain he is in and to allow him to have short periods of time when he could experience a more normal life. The difficulties and lack of success with the procedure means that he has had to give up and has not attempted an exchange for 6 months.	

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	As has already been well documented there is currently no medication available which can provide relief from the pain caused by EPP. Since June 2017, due to extreme constant pain and the anxiety of trying to avoid visible light, my son has resorted to using high strength cannabis in an attempt to make life bearable. This does not reduce the pain but it does make him able to get better sleep and have less anxiety. My son has lost 2 stone in weight and his personality has changed, he is dependent on cannabis and has tried other illegal drug options trying to find pain relief. It is possible that this course of action could kill him but, unfortunately, I cannot stop him as I have no alternative to offer him and have been suicidal myself with the condition. My son and I have met, either face to face at support meetings, or through internet access many people from around the world who suffer from EPP. Every single person has their own EPP my son and I are evidence that the condition differs from person to person but the common symptoms already well documented are consistent across all suffers. There is absolutely no documented evidence to suggest that those with EPP in England require Afamelanotide any less than EPP suffers from other countries. EPP is a unique condition, it is impossible to compare it with any others because they do not exist. All organisations use standardised matrix/guidelines to make decisions about “need”. Therefore it is extremely difficult to obtain any support in the form of Personal Independence Payments or Employment Support Allowance and so people in England with EPP have no treatment and no support. Finally: my son met a young man with EPP. He is American and became so ill with EPP both physically and mentally, that his parents flew him to Europe for an Afamelanotide implant. This was privately funded and something he now does on a regular basis. He is currently in good health, good spirits, he has graduated and is leading a happy life with a good job. I watched him talking to my son who is emaciated from using illegal drugs, scarred from the red cell exchange attempts, in permanent pain, suffering extreme anxiety trying to avoid light and can see no future for himself. This is not something I would wish any parent to have to witness.	
23	I have heard with horror, amazement and incomprehension of your decision to deny the British EPP patients the drug from Clinuvel. Our daughter is also suffering from EPP. We have been looking forward to every rainy day for the past 10-12 years. We and especially our daughter count the days until she turns 18 and finally gets the implant. There are only 356 days until her birthday :-) How can you make such a decision? I am describing to you some situations from the past years that I could not relieve my daughter, I could not help my daughter and save her from pain. But you could do this for all waiting EPP patients in the UK.	

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	This first episode does not seem very restrictive, but shows that we have tried to make the best of the situation: during the holidays and on bad sunny days we sat (me with our daughter and her little sister) until about 16.30 in the darkened room watched TV or played games. When the children were younger, they slept at lunchtime, and we went off in the garden or to the playground after dinner. All children had to go home, but our girls were allowed to play outside for a long time (without other children). In solidarity, our younger daughter did not drive with her friends to the outdoor pool! She stayed with her big sister. Our daughter quickly sensed whether it was a good or bad day, on bad days, the skin began to tingle after a few minutes. Then she was not able to cycle to school (15 minutes). I always drove her by car. Physical education in the open air often could not join you and had to look under your special UV umbrella in the shade. In the summer and on bad days, she always wore long-sleeved shirts and long pants. If she wore short clothes, she stayed in the house or had infernal pain in the evening. On school trips, she often stayed in the youth hostel or in other classes, as she could not take part in many actions outside. or she took the pain because she wanted to be with her friends. For me as a mother, the worst thing is to see her cry in pain, scream and suffer. I can't take her in my arms and was not even allowed to comfort her, as my body heat is unbearable for her, as it makes her pain worse. When she fell asleep in the evening with complete exhaustion, she often flinched in pain in her sleep and woke up again, as there was heat in the bed, which intensified the pain again. You certainly have not comforted a child who cried "Mum even my tears hurt me" Even normal things are not possible: look forward to the first rays of the sun => no, they even scare us eat outside in the garden with the family => we go out after 20h, picnicking with friends and family => we do not participate or plan outdoor activities bike tours, sports outside (jogging, hiking, swimming, etc.), sightseeing, city tours, driving when the sun shines in the car, sitting in the classroom or on the bus at the window side, etc I hope and wish that my words will make you reconsider your decision and give the English EPP patients the opportunity for a carefree, ""normal"" and that's the most important point: pain-free (!) life.	
24	"Life of a six-year old girl with EPP: I am a mother of a six-year old girl in Cologne, Germany, describing hereafter our everyday life. This congenital disease just isn't comparable to any other due to the fact that most of the physicians simply don't recognize it. And the patient is left on	

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	his own with his awful pain. I am a nurse and I know one or two things about suffering. My daughter was one-and-a-half-year old when we first experienced the EPP effect to its full extent. And that happened after FIVE minutes in the sunshine! All of a sudden our daughter started to scream, tried to cover her face, while simultaneously scratching her hands. It was a crazy situation for we could not see any reason for such a behaviour. Various physicians were clueless and sent us back home. The girl was screaming all day, crying at the least, she was unable to eat anymore and just couldn't calm down. Even the nights couldn't give her any ease, she kept whining, too tired to cry. This situation lasted five whole days, we were desperate and going mad. On the second day in bed and not exposed to any sunlight my daughter's face was completely swollen. She could hardly open her eyes. Her nose and lips were just as swelled, as if she had been in a brawl. Arms and hands were swollen, too, her little body just looked bizarre. Again, we desperately looked for help but the physicians couldn't offer any solution. Nothing helped ease the pain - no painkillers, - no cortisone - no antihistamine. NOTHING worked. The kid kept crying all day long. On the fifth day she started blistering, her lips, nose and forehead, even her hands were covered with blisters. The physicians were completely perplexed. This was our first encounter with EPP, unfortunately just the start of an endless story. As a mother of a five-year-old kid I started investigating, hoping to relieve my daughter's suffering, somehow. And ended up with a physician, some 300 kilometers away, who diagnosed EPP. We now know that illness's name but the suffering is still urgent. Our child's life is extremely limited, she simply can't enjoy a normal childhood. She is unable - to go to any birthday party during the summertime, - to go to the beach - to play outdoors - to participate in any kindergarden activities	

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	At this young age, isolation has already begun at her young age. We, her parents, dare not imagine what her future will be like.	
25	I am suffering from EPP and do not understand how patients can be denied a medication that will make their life bearable. Bright light or sunlight for only a very short time lead to unbearable pain. Every part of the skin becomes extremely sensitive against heat and cold. No sleep, only extreme swelling that disfigures you. For 65 years I have endured this, and it has shaped my whole life. I was alone and excluded. In 2017, I got 4 Scenesse implants, and NOW I FINALLY KNOW WHAT LIFE REALLY MEANS! I do not want to go back, ever. PLEASE, make Scenesse available to everyone, so nobody has to suffer needlessly anymore.	
26	Last year, in 2017, I was implanted four times with Scenesse, and it has changed my life almost completely. I was able to tolerate much longer exposures to (sun) light, and that even on consecutive days! This does not mean I am free of any phototoxic reactions, but it's SUCH an improvement! Biking to work, going shopping or going for a longer hike outside, all that is possible now! So the overall result is positive: while Scenesse does not protect from every phototoxic reaction, is very effective in lowering the pain intensity, and making the pain subside very fast.	
27	When I heard and read that the NICE plans to not make Scenesse available in the UK, I could not believe it, are you even aware of what you are doing? I am 42 years old, have been diagnosed only 5 years back, but have been suffering from EPP for all my life - and especially as a child, life with this disease is HELL! You cannot go outside to play, you cannot make friends, because you are socially isolated, and you are constantly AFRAID! And NOTHING helps against the pain! Imaging someone holding your hand in boiling water! THAT is what you are condemning every EPP patient to! You say that Scenesse is not effective. Let me tell you from a patient's perspective who has had the medication: it is more than just "effective"! I was implanted for the first time in my life this year, and where before I could bear only minutes of light on a summer's day, I can now go outside for SEVERAL HOURS EACH DAY! Not just a few minutes, but HOURS! If that is not an improvement, I do not know what is this medication has changed my life! For the first time I could sit in a café, I was able to take a walk outside with friends, without the constant fear of being exposed too much and being awake the following night because of the searing pain. Before, sometimes, you just ignore the warning signs, because you do not WANT to be alone anymore. And you dearly pay for it!	

Individual number	Comment	Response
	I do understand that clinical research in rare diseases is difficult, but if you do not have enough data to make an informed decision, then PLEASE wait for the data being gathered now, and I can tell you, it will make clear how well this medication works! Please do not take away the patient's ONLY opportunity for a somewhat normal life! Imagine your child or your parents suffered from this and then ask yourself if it is ethical to deny them everything you yourself take for granted! Thanks a lot for listening,	
28	"(..) I am 62 years old and although the symptoms began in my childhood, I was 50 years old when I was diagnosed with EPP. After the diagnosis I found the patient association and was lucky to be part of the first double-blind clinical trial of Scenesse in Dusseldorf. When I was getting the non-placebo implant, the summer was a wonderful and I enjoyed it with all my heart. Suddenly I was able to take a walk or ride a bike in the sunshine just like a normal person, without fear of EPP symptoms. During those weeks I did not have to stay alone at home to protect myself from the sun. Unfortunately it took several long years, before the medication was available again - last August I got my first implant, and would not want to miss it anymore. You do not feel isolated any longer, and there's no more sleepless nights due to the pain. I hope every patient will get access to Scenesse as soon as possible.	
29	Deciding not to recommend a life changing medication for people suffering from EPP would not be nice but nasty. I am suffering from EPP myself. A few years ago, I had the chance to try the new medication called Scenesse (Afamelanotide) myself during a clinical trial. Before this I really suffered from EPP. I could not spend my daily life outside like other people. Even normal activities like picking up my kid from school, spending some time at a playground, in our garden or simply doing the groceries always have been a challenge as soon as there was too much light involved. Extra activities, like bicycle tours, open swimming pools and holidays were impossible for me. Light was my enemy and pain was my unpleasant companion. When I started to take Scenesse medication it changed my life. I was able to do all these normal things with my kid. Walking on the sunny side of the road and the sunny side of life! It was incredible for me! I was even able to drive two hours per day in my car to attend a study course. This great time with a nearly normal life ended after the trial was finished. The EPP pain is back and I am suffering again. Now I have two kids, one of them severely disabled. And the new challenge is to cope with EPP having a kid that won't understand why mommy can't go outside.	

Individual number	Comment	Response
	I am now waiting to get treated with Scenesse again. Want to get back to the sunny side of life on the sunny side of the road! Here in Germany I have a realistic chance that this will become reality. However, people in the UK won't have this chance if you refuse to recommend Scenesse as a treatment for EPP patients in the UK.	
30	You are responsible for the treatment and a better life for people in UK, who are suffering because they have the very severe disease: EPP. (…) mother of a daughter suffering from EPP. She is now 24 years old and has been getting the treatment for more than 3 years, first in Switzerland, now in Berlin. And I quote her, when I tell you: She has got a new life. Only with this medication she could survive all the demands in learning to be a nurse in the University Clinic in Cologne and can work every day! And after terrible times in her childhood, she has now a life without pain and social isolation. Because her two elder sisters do not have this disease, you can be sure, that I am a good judge of life in childhood when a person is suffering! No living in the light is possible, social isolation in summer has an end, because she couldn't play outside, couldn't take part sporting activities, has no chance to be part of holiday activities in the summer and all the year outside. Meeting friends is an important factor to become a strong person. We as family are happy, that she grew up with love and help in our family but it is no comparison with life with "Afamelanotide". Indeed, she has a new life!!! And as the President of the German Board, I got to know many comparable stories of German patients, children, adults, old people, male and female. Not rarely, depression, problems with drugs, alcohol, addiction, and suicide are combined with this disease. And I am so happy, that in German Health Policy all responsible people after considering the facts said "yes" to helping all suffering people, making this medication accessible to all patients. What is the problem in UK????? Even the UK did sign the International Human Rights many years ago. And it's a human right to live without suffering if it's possible. And I think in your Health Policy one point is: Quality of Life!!! Please reconsider your vote!!!!	
31	I am a patient suffering from EPP for now 40 years, I am in the absolutely lucky situation to get Scenesse since last year. I	

Individual number	Comment	Response
	couldn`t imagine that I can stay some time in sunlight without having indescribable pain due to the sunlight. Due to the wonderful medicine Scenesse I can feel first time in my live that the sunlight can create a warm and fine feeling on my skin. If someone told me that, I would never have believed it, but it is absolutely true. So please allow the British patients suffering from EPP to have that outstanding, wonderful and only medicine Scenesse for their life. They just want to live a normal life. Please consider this on your decision.	
32	As a patient suffering from Erythropoietic Protoporphyria, I was part of the Phase III, double-blind, placebo-controlled study of Scenesse, at the University Dusseldorf. The medication was implanted into my skin, and after only a few days, I could feel the effects, that would last for 6-8 weeks. For the first time in my life, sunlight felt warm on my skin, and did not cause any pain. Since birth, I have been suffering from EPP, like my mother. Since there were no visible symptoms, we were often misdiagnosed as malingerers. Neither friends nor relatives would believe me, and proposed that I was only imitating my mother. For decades, my disease was misdiagnosed due to missing knowledge on the physician's side, who also banalized my symptoms. Only at the age of 36 (in 1999) a dermatologist finally diagnosed EPP. He sent me to the Dermatology of the University of Dusseldorf. At that time, there was a longitudinal trial going on, investigating EPP and its possible treatment. I took part in that study, and for two years, I was given different medications, including beta-carotin, Vitamin C, Vitamin E, Lysine, but none of that worked. EPP is a highly impairing disease when it comes to quality of life: during the summer months, there's no activity outside possible. Every step in the sunlight is overshadowed with fear and worry. Tinted car windows, sunshades, or similar things do not provide enough protection from the light. Even short term exposure to sun or light in general, also when its overcast, induces the symptoms: it begins with itching, rising skin tension and over time turns into extreme, burning pain and swelling of the skin. Even the strongest pain medication does not alleviate the pain. The symptoms subside only slowly, this takes days. And during that time, your perception of cold and heat is massively disturbed. Normal room temperature of 20Â°C as well as water at body temperature is perceived as burning hot, and will intensify the burning pain. Cold tap water fells like ice, and lower room temperatures lead to a freezing feeling and shivering. In the winter months the symptoms are less frequent. Depending on weather and light intensity, the risk for phototoxic reactions gets bigger with the beginning of spring and stays with me until late autumn. The first problems will turn up on parts of the skin that are exposed the most (face, head, ears, lower arms, elbows, hands, calves, knees, feet). The only way to stay safe is to keep to inside rooms. If you cannot prevent outside activities, or long drives with the car, I try to protect myself by wearing a baseball cap, long-sleeved tops and trousers, gloves, socks and closed shoes. You can imagine it's a torture during summer. Strange looks from other people I have learned to ignore.	

Individual number	Comment	Response
	Scenesse would so much improve quality of life for me!	
33	I am a 51 year old suffering from EPP and will tell you of my tale of woe, so you can better understand what massive, painful, mental and physical effects EPP has on my entire life! Since I was young I would get extreme pain after sun exposure, like sunburn but much stronger, ad holding for days. Most of the time you do not see that there's ANYthing wrong with my skin but it feels like burning myself! Not one painkiller helps against the terrible pain. You can relieve a bit of the pain by using cold water, cool packs, cold poultices and the retreat to a dark, cool room inside. I endured countless visits to the physician, but got diagnosed as a malingerer since there were no visible symptoms. So I did no longer go to any doctor. I withdrew myself more and more, became isolated and was more often than not the odd one out. There were no outside activities with friends, like swimming, biking or any other kind of sports, and even my daily route to school was very painful. And picking a job was difficult as most of the professions I was interested in were a no-go: farmer, florist, veterinarian or architect. When I was 20 years old, I finally got the right diagnosis: I suffered from the rare metabolic disorder Erythropoietic Protoporphyria (EPP) and not a simple sun allergy. Finally the problem had a name and I had hopes to find a cure or at least some relief. The dermatologists in the university in Dusseldorf and I tried everything without success. So, another let down, more frustration, doing the best despite the problems, more isolation, more loneliness. Only wearing long-sleeved clothes made from tightly spun cotton, jeans, jacket, hat, gloves and using an umbrella helped me survive everyday life. During the worst times, I wore a cloth hiding my face. But even that would only protect me for a short time. And you are sure to attract stares from everyone. I have adapted my whole life to my disease. And as a mother of three children, all problems repeated. There no way to go to the playground with them... Joining my kids on their way to kindergarten or school was problematic, and being with them on school trips or events impossible most of the time. For me, there were no holidays at the sea, in the mountains or in the south, no going to the swimming pool, not until today. My kids were able to do all this with friends of ours. But I was alone, in the dark, wanting to share these memorable moments WITH them. Since June 2017, I am being treated with the only medication that helps if you have EPP: Scenesse. I have not had ANY side effects, and I am overjoyed and so relieved! My life has changed massively to a really good end:	

Individual number	Comment	Response
	after I started getting Afamelanotide, - I was able to make a bike tour during summer for the first time in my life - I was able to travel to work without the protective gear I described above, or just be outside - I was able to work in the garden, go for a swim, bike, hike, and simply enjoy nature - I seldom feel pain, and if I get too much sunlight and do feel pain, it is gone the next day - I can be with my friends when they do something outside in summer - I do not have to separate myself from others - I am much less often alone, and I am more sociable and cheerful - I can do sports outside After 51 years, this treatment enables me to live an almost pain-free, normal life! Finally, a life worth living, a life fit for a human being! For me, the denial of treatment with an already approved medication constitutes a failure to render assistance as well as a form of criminal assault on all EPP patients in the UK. After all you just heard about the positive effects of Afamelanotide, can you really stand by your decision with a clear conscience? With that decision, you will be complicit in causing more pain and harm we EPP patients already have enough of! Every single EPP patient has a moral right to that treatment, since it is proven to be effective and has no side effects. No government agency should prevent patients from obtaining this treatment!	
34	"I am a 53-year-old patient, suffering from EPP, like my older sister. And when I say “suffer” I mean it. Up to this day, dealing with this disease was excruciatingly painful. No matter whether it was as a child or an adult, the disease demands limitations and adjustments to your life, always. I really could have done without these painful experiences, but I could not simply go into the next shop and buy a new body! So I always had to take my handicap into account when planning my life. Unfortunately EPP is not my only handicap, but the most severe, since it limits my life’s choices: It is horrible if you cannot make friends as a child! It is horrible if your disease limits your choice of profession!! It is horrible when your personal happiness is being governed by a disease!!!	

Individual number	Comment	Response
	It is horrible to suffer from EPP if there is a medication for it!!!! It is horrible that even in this enlightened and wealthy time, the arbitrary decisions of some lead to the suffering of many. That people who do not have to suffer indeed have to suffer. This is torture and certainly violates any human rights! To completely list my tale here would be too much, let me say this: EPP is with me 24 hours a day, my whole life through, almost 53 years. If I had not adapted, I would no longer be alive to some degree, the adaptation works, but it comes at the cost of deprivation, excruciating pain and hardship! It is inhuman to deny suffering patient access to this medication! Why? Monetary reasons? This is incomprehensible! Please reconsider your decision about this medication. Otherwise you deliberately deny a suffering person the relief so desperately needed. Please vote for the approval of Afamelanotide in the UK, the only working medication for our condition, a drug that massively improves the quality of life for the patients and has no severe side effects!!!! With kind regards and in hopes for a positive vote from your side,	
35	My son (20 years old) has been treated with Scenesse for the last two years, and his life has completely changed for the better! It took about two weeks after setting the first implant, that the first effects became visible, a slight tan and pigmented moles appeared. After careful acclimatisation to the sunlight (he avoided the sun as much as possible up to that time), he discovered that the sunlight could feel pleasant on his skin after the second implant, the effects got more pronounced, and he was able to go outside without having to worry, he could take his bike to university and take the car on his own. The burden he had been carrying just fell away, and his permanent abdominal pains, symptom of his constant psychological strain simply disappeared. Not needing to explain himself all the time, not needing to abstain from what he wanted made his daily life lighthearted. He simply began to LIVE!!!	

The following consultees/commentators indicated that they had no comments on the Evaluation Consultation Document

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Dr Meindert Boysen
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Submitted through NICE Docs

CC: Marie Manley, Bristows LLP

24 January 2018

Re: Afamelanotide for treating erythropoietic protoporphyria [ID927] – Evaluation Consultation Document (ECD)

Dear Dr Boysen,

CLINUVEL has reviewed the draft ECD in line with the request from NICE of 13 December 2017. It is clear from the Company's review that the Evaluation Committee has made errors in its evaluation, has failed to take all relevant evidence into account, has taken an unreasonable approach in its interpretation of the evidence and therefore has not made a provisional recommendation which is sound and suitable guidance for NHS England.

A preliminary response to the ECD from the Company is appended, along with comments on the release of the Committee Papers. We trust NICE and the Committee will fully review the Company's response prior to the meeting of 20 February.

Yours sincerely,

Lachlan Hay
General Manager,
CLINUVEL (UK) LTD

Attached:
Appendix 1 – Response to ECD
Appendix 2 – Comments on the Committee Papers

Appendix 1 – Response to ECD

1. Has all of the relevant evidence been taken into account?

SCENESSE® (afamelanotide 16mg) is the first product globally to have gained approval for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP). EPP is a rare metabolic disorder which causes phototoxicity (anaphylactoid reactions and burns) when patients expose themselves to light. We have set out in detail below our concerns that NICE has not taken into account all the relevant scientific evidence in its ECD. See also the comment in Appendix 2 regarding the apparent omission by NICE within the Evaluation Committee (hereafter the "Committee") papers of the document appended to the Company's correspondence of 06 November 2017.

1.1 Evaluation of clinical effectiveness

The ECD raises questions as to the clinical effectiveness and benefit of SCENESSE® to EPP patients and does not appear to have taken the evidence provided by the Company, the patients or the expert physicians into account.

Specific examples of statements within the ECD which show that NICE has failed to take into account evidence regarding the effectiveness and benefits of SCENESSE® are set out below, together with the Company's comments.

> ***"Clinical trial results suggest that afamelanotide may be effective. But it's unclear how effective it is, whether the effectiveness varies from person to person and how it affects quality of life."*** (Section 1.2) (emphasis added)

However, the lack of clarity alleged by the ECD seem incomprehensible since expert clinical and patient evidence and compassionate use have shown the effectiveness of the drug and the impact on patients' quality-of-life (QoL), which were recognised by the EMA and the EU Commission in granting marketing authorisation. This expert clinical and patient evidence has been discussed in detail within the European Public Assessment Report (EPAR).

> ***"… committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials."*** (Section 4.7) (emphasis added)

There is sufficient evidence to show that both clinical and patient experts know that the clinical benefit seen is greater than that reflected by conventional or clinical trial analyses and evaluation, rather than simply believing this to be the case.

> **"*The committee noted that patient testimony about afamelanotide reported much better outcomes than the clinical trials… The committee considered the possibility that these testimonials were not reflective of all patients' experience on afamelanotide because it had not been presented with any data indicating that these were a representative sample of everyone who had had afamelanotide. The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear.*"** (Section 4.8) (emphasis added)

These patients and clinical experts were selected and considered representative by the EMA Committee for Medicinal Products for Human Use (CHMP) during its review process and NICE has no evidence on which to consider this not to be the case. In addition, the Company has had no influence over the number and type of patients and clinical experts who were invited.

> ***"… it noted that it had not been provided with any data showing how the reduction in phototoxic reactions seen with afamelanotide affected peoples' ability to work or study. The committee was aware that the company had provided exploratory analyses on loss of earnings associated with EPP, but it was unclear what the data underpinning the company's assumptions were. The committee concluded that afamelanotide would have an impact beyond direct health benefits but that the extent of this impact was unclear."*** (Section 4.19)

Paragraph 43 of the NICE HST Guidance[1] states that in NICE's deliberations they must take into account the impact of the technology beyond direct health benefits. Additionally under paragraph 41 of the Guidance the Committee is required to consider "*any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition*". Therefore, by concluding that, due to lack of quantitative data, the impact beyond direct health benefits is unclear, it demonstrates a failure to take into account the relevant qualitative evidence.

> "***The committee noted the possibility that deeply ingrained light avoidance behaviour may have influenced the trial results. However, it was aware that this alone may not explain the huge gap between expert testimonies, anecdotal evidence of those present at the meeting and the trial results.***" (Section 4.20)

While the Company agrees that there is a difference between the efficacy demonstrated in clinical trials and the overwhelming clinical effectiveness derived from the clinical statements, reports and testimonies of patient and clinical experts, the Company has consistently noted that there is a lack of scientific tools and instruments to fully measure and capture the impact of EPP, light deprivation, and/or a photoprotective treatment. Indeed the EPAR clearly noted that the lack of scientific tools and instruments was a determinant factor in the product's final approval under exceptional circumstances (EC), since it was not possible to generate the clinical evidence required. Further, the EMA CHMP convened an Ad-Hoc Expert Group Meeting in 2014 as part of the marketing authorisation assessment procedure (which is discussed at length in the EPAR) and which recognised the challenges posed in evaluating EPP and the collection of evidence, concluding:

> *"In this setting the randomised controlled trial appears to be a less effective tool for determining treatment effects… In all 5 clinical trials of various designs it has proven impossible to accurately record the increased clinical freedom and loss of risk aversion reported by the majority of patients and physicians. Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease and 'visible light' to exposed skin. It is also conceivable that the complexity of the EPP patients* (sic) *behaviour and the dependence of phototoxicity with environmental factors in real life differ to such an extent that the actual benefit cannot be captured in conventional clinical trial designs…"* (Pages 89-90).

In addition to the above specific points, significant submissions were made by the Company regarding the clinical benefit provided by SCENESSE® to EPP patients who received it that appear not to have been fully taken into account. A marketing authorisation granted under exceptional circumstances, by its nature, shows that despite the marketing authorisation holder's inability to collect the comprehensive data normally required to obtain a marketing authorisation (i.e. data to demonstrate the safety and efficacy profile of an authorised product in its target indication) the medicinal product is nonetheless considered efficacious and to have an acceptable safety profile. While the ECD notes the EC approval (section 3.1), both the Evidence Review Group (ERG) and the Committee have failed to take its significance into account in all of their documentation, to acknowledge the uniqueness of the EMA CHMP conclusions, or to incorporate the evidence that the EMA CHMP used in their review of SCENESSE®.

The ERG, Committee and ECD also fail to recognise that it would be unreasonable to request or expect the Company to provide data which are impossible for the Company to obtain due to the ethical and scientific limitations around the conduct of clinical studies (which the EMA CHMP recognised and accepted). This is

[1] Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes

particularly the case in light of the fact that the EMA concluded that there was sufficient evidence to grant a marketing authorisation under exceptional circumstances. In addition, given the ruling of the Court of Appeal in the case of *Servier v NICE*[2] it would be a misapplication of NICE's powers to re-open the conclusions of the EMA CHMP without a valid justification for doing so. Therefore, NICE must adequately and properly take into consideration the evidence considered by the EMA CHMP regarding the effectiveness and clinical benefit of SCENESSE®.

1.2 Quality of life data and tools

The ability to capture and quantify the impact of EPP on patient quality of life is discussed in the ECD.

> "***… the company had developed a condition-specific quality-of-life questionnaire called the EPP-QoL, but that this had not been validated… The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that people with the condition and their clinicians report as important. It also concluded that, without appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture any treatment benefits with afamelanotide.***" (Section 4.9)

> "***The committee noted that the ERG considered that, although not perfect, the DLQI addresses some factors that impact on the quality of life of a person with EPP, such as pain and ability to work or study. The committee heard from the patient experts that the DLQI includes questions that are not relevant to EPP… DLQI does not ask anything about exposure to light, unlike the EPP-QoL. Furthermore, the company stated that the DLQI does not ask about feelings of anxiety… The committee was also disappointed that available SF-36 data had not been presented by the company because this measure includes questions on fatigue and anxiety that are not captured by the DLQI.***" (Section 4.10)

The focus of the Committee was on the appropriateness and omission of pain, work and study from the EPP-QoL and the preference for the DLQI. However, having taken extensive expert advice in the UK and globally on this point, the Company's clear position is that the DLQI is not appropriate to capture the QoL of patients with EPP. The suggestion that the DLQI may be able to 'address some factors' in capturing EPP is very far from a finding that the DLQI is able to accurately capture the impact of the disease on patients, and thus the impact of treatment. As a matter of fact the DLQI has been deemed unsuitable by the global experts in porphyria to capture the impact of EPP, and this position led to the attempt to develop a disease-specific instrument. The Company's position is that because the DLQI is a short-term evaluation (i.e. discussing "the last week" of a patient's experience) aimed at general skin disorders rather than the severe complexities of the lifelong condition EPP, the DLQI is in no way sensitive enough to truly capture the full impact of the disease – unfortunately, currently no tool/instrument is.

It appears that the Committee has not fully taken into account the reasons why the EPP-QoL would be more suitable than the DLQI. The reasons for this are briefly summarised below:

- It appears the Committee is taking a contradictory position, as they dismiss the EPP-QoL for supposedly omitting two issues relevant to EPP ("pain" and "work or study") but accept that the DLQI despite its very broad focus on the impact of a patient's skin (EPP is not a skin condition, and the Committee learnt from patients and expert physicians that the restrictions in the disease are largely due to environmental and artificial light exposure) and lack of focus on EPP-specifics.

[2] *R (Servier Laboratories Limited) v National Institute for Health and Clinical Excellence & Anr* [2010] EWCA Civ 346 (on appeal from QBD Administrative Court). The Court of Appeal held that a decision of NICE should be quashed on the grounds that it lacked adequate reasoning and the court had 'grave concerns' about its rationality. In particular, the decision of NICE not to take into account a particular clinical trial when assessing the effectiveness of Protelos was quashed.

- While "pain" is a clinical symptom of EPP it is relatively rare that an adult patient will actually experience "pain'' since they will have adapted their lives to avoid it. Therefore measuring "pain" will yield no results of any significance, hence why it was not included in the EPP-QoL. Pharmacologically, within the field it is accepted that "pain" is a surrogate description of phototoxicity for which the medical nomenclature is currently lacking.
- Anxiety has been dealt with in the EPP-QoL by the inclusion of the question "*how often did you feel you were at risk of developing EPP symptoms?";* however, questions on fatigue were not addressed as they have not always been seen as a clinical symptom (as has been the case for many medical conditions) and the EPP-QOL was used prior to patients starting to raise awareness of the issue of fatigue (i.e. pre-2014).
- SF-36 data were gleaned from the CUV017 study by the ERG. The CUV017 study is not considered pivotal by the Company but forms only part of the evidence base; however, to use the SF-36 data from this study alone as a basis for the ERG evidence is not representative of the clinical program or the disease of EPP, nor is it a rational approach.
- It is not correct to say that the EPP-QoL has not been validated, since it has been partially validated. The Company has always presented that this tool is partially validated, and this is also stated in the Biolcati et al (2015) paper. Additionally, due to the lack of scientific tools to measure the effects of EPP (as set out above) there is long-standing evidence that standardised tools are inappropriate for quantifying QoL in EPP (see the Rufener, 1987 paper).
- Later in the ECD it is noted that DLQI "could capture some of the key aspects of EPP" (Section 4.10), but this is not elaborated on, leaving one to speculate on NICE's rationale for the use of the DLQI and demonstrating a lack of understanding of EPP.

Therefore, it appears that the Committee has concluded that the DLQI model would be preferable based on a misunderstanding of some crucial aspects of the disease, its symptoms and the EPP-QoL model.

2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

The Company is concerned that NICE has not taken a reasonable interpretation of the evidence regarding clinical effectiveness or value for money for the reasons explained in detail below. Had NICE done so it would have reached a different conclusion regarding both the clinical benefit and cost effectiveness of SCENESSE®.

2.1 Evaluation of clinical effectiveness

Further to its failure to take account of the evidence regarding clinical effectiveness as outlined in Section 1.1 above, the Committee has gone on to fail to interpret the evidence presented by the Company in line with the conclusions of the EMA CHMP, with examples provided below in Sections 2.1 and 2.5--2.6. The Committee is re-opening the conclusions of the EMA CHMP without providing a valid reason for doing so or acknowledging the evidence provided to it by the Company regarding clinical effectiveness.

As explained above, according to the Court of Appeal in the case of *Servier v NICE*, if a regulatory authority has assessed the data and on that basis granted a marketing authorisation, NICE must justify any departure from it. Therefore, it will not be acceptable for NICE's assessment to be 'similar' to that of the EMA, rather the EMA's conclusions on the data must be accepted by NICE unless NICE can justify, on the basis of evidence, taking a contrary interpretation or departing from it.

The ECD notes that:

> **"*The committee noted that its remit included an independent assessment of the benefits and costs of afamelanotide. It also noted that the EMA considers the potential efficacy of a technology in relation to its safety,* (sic) *The committee, on the other hand, considers the potential benefits ('effectiveness'), costs and uncertainties around recommending mandatory funding of a technology (in this case afamelanotide) within the overall objectives of the NHS to maximise health gain from limited resources. The committee concluded that it was appropriate to consider the clinical effectiveness of afamelanotide, and the uncertainties in the evidence base, in its decision-making*."** (Section 4.6)

NICE's interpretation of the evidence supporting the grant of the marketing authorisation (i.e. the expert physicians' and EPP patients' testimonies) is departing from the interpretation of the EMA. Furthermore, no justification has been provided for NICE doing so. Therefore, following the principle set down in *Servier v NICE* (detailed above) NICE appears to be not only acting unreasonably but also *ultra vires*. In order to assess the cost effectiveness of SCENESSE®, NICE should rely on the real-life evidence provided by the patients and clinical experts regarding efficacy, as there is no other way to appropriately interpret the evidence regarding the effectiveness of SCENESSE® for all the reasons explained above (and in previous correspondence).

The ECD also states:

> **"*The committee noted that patient testimony about afamelanotide reported much better outcomes than the clinical trials... The committee considered the possibility that these testimonials were not reflective of all patients' experience on afamelanotide because it had not been presented with any data indicating that these were a representative sample of everyone who had had afamelanotide. The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear.*"** (Section 4.8)

The Committee was presented with consistent evidence by the Company, patients and expert physicians that most patients and expert EPP physicians reported, anecdotally, a larger clinical benefit than that shown in clinical trial data, partially due to the lack of scientific tools and instruments available to measure EPP (see Section 1.1 of this document). This also formed the basis for EC approval from the EMA CHMP. It is not

reasonable to take an alternative interpretation of the data within the EPAR regarding the value of the expert evidence, not just as evidence of the impact on the patient but also as proof of efficacy of the product.

Further, the ECD notes elsewhere that:

> ***"The committee asked if there was any evidence about how the severity of EPP affected outcomes with afamelanotide, and heard there were no specific data on this. However, the clinical experts suggested that, anecdotally, afamelanotide had been effective across the <u>whole trial population</u>"*** (Section 4.7) (emphasis added)

In its HST guidance NICE recognises the particular circumstances of orphan diseases, including the potential limits regarding the nature and extent of evidence available, and the Committee is required to consider "*any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition*" (Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes, Paragraph 41). Therefore, it is not reasonable for the Committee to interpret the data provided as failing to indicate the representativeness of the patient and clinician testimony. Further, it is reasonable to interpret that whilst the true extent of benefit has not been demonstrated clinically, it is undoubtedly greater than that shown in the clinical trials, as evidenced by patients and healthcare professional testimony.

It is noted that the EPAR does take account of the role qualitative data submitted to CHMP played in its evaluation of the efficacy and clinical benefit of SCENESSE® for EPP:

> *"Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse."* (Page 102)

2.2 Interpretation of disease

The ECD notes:

> ***"EPP is a cutaneous porphyria, and the major symptom is hypersensitivity of the skin to sunlight and some types of artificial light. This causes phototoxicity (a chemical reaction in the skin), and the skin may become painful, swollen, itchy and red."*** (Section 2.1)

These statements show a clear lack of understanding of the disease by the Committee. Consistent with the Company's submissions, the major clinical symptom in EPP is phototoxicity, which is not a sensitivity to sunlight but a chemical reaction to visible light (Soret Band peaking at 408 nanometers) *underneath* the skin. This lack of understanding is likely to have influenced NICE's interpretation of the clinical evidence provided, in particular in reaching the conclusion that the DLQI is an appropriate tool to measure QoL.

The ECD notes:

> ***"… a relatively small but statistically significant increase with afamelanotide in the amount of time a person could spend in daylight without pain, and a decrease in the number and severity of phototoxic reactions"*** (Section 4.7), and
>
> ***"The committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen in the trials".*** (Section 4.7)

During the Scientific Workshop of 23 March 2016, from the submissions of the Company, patients, and expert clinicians and at the Committee Meeting of 24 November 2017 the Committee was made aware of the restrictions EPP places on patients with regards to their ability to expose their skin to light/sun. While the data captured in clinical trials may seem trivial to members of the Committee, the patients and physicians clearly stated that:

1. Even brief light exposure without the risk of phototoxicity presents a significant improvement to patients' quality of life; and
2. The data captured in clinical trials for direct sunlight exposure was a proxy measure, which indicated a potentially greater effect when considered in the context of artificial, indirect (dappled) or reflective light exposure.

The attempts to trivialise the increase in the amount of time patients were shown to spend in direct light shows a lack of understanding of EPP and its impact by the Committee, and the failure to give due weight to this evidence shows that the Committee's interpretations of the evidence provided have not been reasonable and decisions made based on the Committee's disease understanding may have been arbitrary in nature.

The ECD notes:

> **"*The committee concluded that there is some variation in how long people with EPP can be exposed to sunlight without a reaction, but the range across people diagnosed with EPP in England, and any variation in patient experience of the condition, was unclear because of a lack of data*."** (Section 4.5)

Throughout its submission the Company has highlighted the variance of the disease and the effect of conditioned behaviour, the priming phenomenon, and prodromal symptoms unique to EPP patients (the latter two were recognised in the Committee Papers but not by the ECD). The inability to quantify disease variance, however, is not due to a lack of data, but rather a lack of scientific instruments and tools to measure the disease. This issue is discussed in Section 1.1 of this document. In other words, it would not be possible (on the basis of current science) to measure any variation in patient experience of the condition, and therefore it is not a reasonable interpretation of the clinical data to expect this to have been possible to provide.

2.3 Long term efficacy

The ECD raises questions regarding the ongoing clinical benefit of SCENESSE® for EPP patients:

> **"*However, the committee also heard that, in the long-term observational study (Biolcati et al. 2015), there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials*."** (Section 4.7)

Contrary to this statement, Biolcati et al (2015) states:

> *"We therefore conclude that afamelanotide treatment strongly improved QoL in these patients, likely due to mitigated light intolerance."*

It is unclear how the Committee has come to a contradictory conclusion, and the comment in the ECD does not reflect the Company's minutes of the meeting of 24 November 2017. Therefore the Committee's interpretation of the evidence presented on long-term use and clinical benefit is not reasonable.

2.4 Drug mechanism of action

The ECD notes:

> ***"Afamelanotide works by increasing melanin in the skin, which makes the skin tan, giving some protection against light damage."*** (Section 1.2)

The Company would note that afamelanotide *activates* melanin production. Melanin absorbs and scatters light as a filter as well as scavenging free radicals and activated oxygen species, providing photoprotection in EPP patients. Therefore, the tanning effect is a biomarker of the drug, rather than the sole protective element, and so it appears the Committee has misinterpreted and/or failed to understand the true mechanism of action by which the drug works. It is obvious that the Committee has failed to understand the systemic effect of the synthetic hormone on the integument in EPP.

2.5 Melanogenesis

The ECD appears to raise concerns on blinding in clinical trials based on the pharmacodynamic effect of afamelanotide (melanogenesis).

> ***"… some patients may have known they were having afamelanotide because it caused their skin to tan."*** (Section 4.6)

This concern was addressed by the Company in its responses to the ERG and was accepted by the EMA CHMP in the EPAR as not having any impact on the perceived effect of treatment. In short, a skin colour change *per se* would not have led to a change of behaviour as patients would not consider a skin colour change to equal protection. This is in part because beta carotene treatment (a previous proposed treatment tried by EPP patients) would also lead to a skin colour change but did not equate to effective treatment. The EMA CHMP did not consider that unblinding would have biased the study results. Therefore, it is not reasonable for the Committee to diverge from this opinion in its evaluation and interpretation of the evidence provided.

2.6 Clinical data

The ECD notes:

> ***"The committee noted that the Good Clinical Practice inspection conducted by the European Medicines Agency (EMA) highlighted concerns with CUV029 and CUV030, including unsatisfactory collection and analyses of data."*** (Section 4.6)

The Committee fails to recognise the outcome of the EMA CHMP's decision on the same issue, which is noted in full in the EPAR:

> "*Due to GCP non-compliance the efficacy data from these trials were not considered pivotal for the assessment. However, as pointed to by the Applicant there is an unambiguous trend for a positive effect (primary endpoint) in all these two clinical trials CUV029 and CUV030 (and in CUV039, see below). The effect size in the trials appears to be small, but a beneficial effect seems apparent."* (Page 85)

Additionally, the EPAR states:

> "*Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse*." (Page 102)

Therefore, the EMA CHMP were reasonably convinced the trial data showed the effect of SCENESSE® and that this effect on EPP patients was positive. Again, in line with the *Servier v NICE* decision, it is not reasonable for the Committee to raise the issue of GCP compliance in clinical trials without acknowledging that the clinical trial results and trends were in line with the conclusions of the EMA CHMP, or to misinterpret the GCP issues as having an effect on the demonstration of efficacy.

2.7 Commercial in confidence information and intellectual property

The ECD notes the Committee's disappointment that the Company considered its model to be commercial in confidence (Section 4.11). The Company noted in correspondence to NICE that the Company:

> *"… has focused more than a decade of R&D efforts on SCENESSE® (afamelanotide 16mg) as the first ever therapy for the ultra-orphan indication erythropoietic protoporphyria (EPP). The Company spent more than 2.5 years developing the DALY model for EPP which, per your correspondence of 10 October, is indeed novel. As a single product company, the DALY model forms part of our intellectual property and the company is not in a position to enable its publication in full."*

During the Committee meeting of 24 November, the Company reiterated that the model forms part of its intellectual property and that its reliance on a single commercial product after more than a decade of development meant it was reasonable to maintain confidentiality of the model. This is a legitimate and important position for the Company to take, and not one that would have any impact on the interpretation of the relevant data by the Committee, nor would it be reasonable or appropriate to treat it as such.

2.8 Economic model (value for money)

The ECD notes on several occasions its preference for models other than those proposed by the Company, for example:

> **"*The committee noted, however, that it could consider non-reference case methods alongside those in the reference case if there is a strong case for it. However, it was not persuaded by the theoretical argument for preferring an analysis based on the DALY to one based on the QALY. In addition, the committee considered that it had not been provided with evidence that the data on which disability was assessed were more robust than the data on utility*."** (Section 4.12)

The Company notes that there is a lack of guidance as to when non-reference models should be accepted, resulting in non-transparent and arbitrary decisions being made on this matter by NICE. Further, the Company clearly outlined in its correspondence to NICE that the use of inadequate tools by the ERG to develop a QALY model was invalid and unreasonable, consistent with the lack of scientific tools and instruments available to measure EPP (see Sections 1.1-1.2 of this document). Further, the Committee notes in section 4.12 of the ECD that its preference for the ERG model has little bearing on the overall use of DALYs vs QALYs, despite the ERG model then arriving at significantly higher ICERs than those proposed by the Company (i.e. the difference between £1,785,957 and £278,386). As an underlying rationale for the Committee's final recommendation, the Company would argue that this is not a reasonable conclusion.

The ECD notes:

> ***"The committee considered that this approach provided a more direct link between quality of life measured in patients in the clinical trials and the modelled benefits, and with fewer assumptions than the company's proxy-condition base-case approach."*** (Section 4.14)

Despite acknowledging that the quality of life measured in patients in clinical trials does not reflect the actual impact of either the disease or its treatment due to a lack of scientific tools and instruments available to measure patient quality of life, the Committee takes no measures to mitigate this in its approach, rather preferring to adopt the ERG models as "more plausible". To acknowledge and yet ignore that the evidence being selected and relied upon is arbitrary, and the preference for the ERG model and the interpretation of economic value on that basis is not reasonable in the context of EPP or the findings of the EMA CHMP.

The ECD notes:

> **"*The clinical experts stated that they expected the implants to be used from around March to October in England, meaning that 4 implants would be used, but that some people may not need the maximum number. The committee noted that the company had provided an estimate of the average number of implants people with EPP may have, but has provided no detail on how this average was determined and whether it was generalisable to people using afamelanotide in clinical practice in England."*** (Section 4.16)

Appendix 1 to correspondence sent to NICE on 02 October 2017 (included in the Committee Papers) clearly outlines the rationale for the average number of implants used in the Company's model:

> *These data don't originate from or reflect data on the average number of implants per year from clinical studies, but originate from CLINUVEL's experience in distribution of the product in a compassionate use/expanded access context and also commercial distribution of SCENESSE® in EPP (i.e. 'real world' use).*
>
> *Per table A2 of the CS:*
>
> Average dose of [redacted] implants per year seen in treatment to date.
>
> *Per section 12.1.5 of the CS:*
>
> Average [redacted] implants per patient per annum: represents average seen in expanded access and commercial distribution of the drug to date across the expected EPP patient population.
>
> *Per section 12.4.2 of the CS:*
>
> The base case is calculated according to the predicted number of afamelanotide implants received per year (n=[redacted]) according to CLINUVEL data obtained from conditions of use of the product to date.
>
> (CLINUVEL submission to NICE 02 October 2017)

It is unclear why the ECD has not acknowledged this and it is not reasonable for such evidence to be omitted. It is also not reasonable to reach a conclusion on economic value based on a misinterpretation of the data regarding implant use.

3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

In its recommendation the Committee notes that "it was unlikely that afamelanotide would be considered a cost-effective use of NHS resources". By misunderstanding the mode of action of SCENESSE® and by failing to take into account all of the evidence provided to the Committee and its unwillingness or inability to interpret the lack of scientific tools and instruments available to quantify EPP or the impact of treatment, the recommendation proposed is not a sound or suitable basis for guidance to NHS England. The Company respectfully requests that the Committee reconsiders all the relevant evidence before the meeting on 20 February 2018.

Appendix 2 – Comment on Committee Papers

The Committee Papers are consistent with the Company's comments during the Committee meeting of 24 November 2017. However, it is unclear to the Company why NICE chose not to include the document appended to correspondence of 06 November 2017 in the Committee Papers as this document summarised the Company's position to NICE, including regarding use and cost of the product. A failure to include this document in the Papers suggests it was not supplied to the Committee and, inexplicably as an essential document, no rationale was given for its omission.

If the document was supplied to the Committee it should, in the interests of transparency, have been disclosed – to the extent possible – as part of the Committee Papers on NICE's website. A redacted version of the document was provided to NICE on 12 December 2017 for this purpose.

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24 January 2018

We, the British Porphyria Association (BPA), are writing in response to the Evaluation Consultation Document (ECD) for Afamelanotide for treating erythropoietic protoporphyria (ID927). This response will address, in turn, the four questions identified within the ECD.

As an organisation we are deeply concerned that, as a result of NICE's proposed recommendation, EPP sufferers within the UK will miss out on a highly innovative first-in-class treatment; one which their counterparts in other parts of Europe are reporting gives huge positive impact on quality of life and the opportunities that Afamelanotide has opened up for them. **We hope that on further consideration NICE will approve or provide a pathway for the approval of the use of Afamelanotide in the NHS.**

1. Has the relevant evidence been taken into account?

We maintain that some of the relevant evidence has not been fully explored.

Patient testimonies: Para 4.8 concluded that there was a 'substantial dichotomy between the patient/clinical expert testimony and the trial outcomes, and the true extent of benefit was unclear.' In the same paragraph, NICE queries whether the positive experiences of Afamelanotide are representative of most of those on the trial. Although trial data in the UK is limited, it is evident from qualitative data that very many EPP patients on the trials benefited tremendously from Afamelanotide. **Patient experience is compelling and should be listened to. It should not be underestimated simply because it does not fit the standard criteria on clinical effectiveness.** This data is supported by testimony from UK clinicians who observed changes in patients first-hand (para 4.7).

By allowing patients to spend longer in the light, Afamelanotide is reported to be extremely helpful in reducing episodes of pain, fatigue, social alienation and other symptoms of EPP. It has been variously reported as 'life changing' or a 'miracle'.

One EPP patient from the UK, who took part in the trial, said:

> *"Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to switch on the TV or look at your phone because every time you do you feel like you are on fire. Imagine not being able to do your job because the office lights cause you pain.*
>
> *That is my day, every day, not just in the summer, but even in winter.*
>
> *Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. I took part in a clinical*

trial for Afamelanotide. My life changed. I went out of the house in shorts and t-shirt, I sat in the sun, I had the best year of my life. I went from suffering to enjoyment with this treatment! I could spend hours out in the sun without pain for the first time in my life.

Now I'm back to hiding, avoiding things, I can't even take my children to school without wearing hat, coat and gloves."

Continuation of treatment despite considerable expense: The draft recommendations do not recognise the fact that international EPP patients, who have been on Afamelanotide for many years, have travelled considerable distance (at significant cost to themselves) in order to continue receiving the treatment (Biolcati et al. 2015 [1]). We would also request that NICE further consider the fact that the vast majority of patients who have had Afamelanotide available to them do not cease taking the treatment. This can only be explained by the treatment making a marked difference to their quality of life.

"Ten minutes passed, then 20, 30, 40 minutes and more in the sun without the typical painful symptoms! After over 40 years with the illness, I finally have something against EPP… this treatment changed my life!"

"For the first time in my life I could accompany my daughter to an athletic competition – and she has won!"

"For the first time I have experienced how pleasantly warm the sun can feel."

"Last summer a miracle occurred – I took part in the Afamelanotide clinical trials – for the first time in over 50 years, I was able to venture to the store without the threat of enduring two days of excruciating pain."

The cumulative/multiplier effect: As recognised in the ECD, there is clearly a dichotomy between trial data and patient testimony (para 4.8), resulting in EPP still being a relatively misunderstood disease. Whilst the pathology is now reasonably well established, measurements of the effects of the condition are still evolving.

In response to the various written documentation associated with the consultation, a number of our members have pointed out one main aspect that is possibly missing in the calculations and studies; specifically, the real benefit from Afamelanotide is not simply the extra minutes it allows patients to spend in light. Whilst this is significant and highly beneficial, with even small gains leading to substantial improvements, importantly, there is also a multiplier effect on quality of life.

Thus, the studies and draft recommendations do not fully take account of the value in avoiding the lengthy recovery periods that follow an EPP event. Given the hours, and sometimes days, taken to recover from an EPP episode, those additional minutes and hours in the sun are not simply the sum of what can be done in those hours (albeit an extremely important gain). It is also the additional work and tasks that could be carried out in the many hours that are lost when an EPP event is triggered. If a small difference in exposure time can prevent a significant reaction and be repeated day after day, even small increments of time spent in light add up to very large returns in terms of productivity and quality of life.

The relationship between extra time in the sun and opportunities to the patient is not simply a 1:1 relationship. Therefore, the true impact of the gain cannot be assessed by simplified 'time in

sunlight' data. Patients may, for example, be able to walk down a shady side of a street, but then need to cross the road, which means exposing themselves to sunlight. Enabling these additional small times in the sun substantially extends how far they can go. The ability to withstand a small extra time in the sun also means that EPP patients are able to withstand considerably longer periods in cloudy daylight or even, for some patients, in artificial light. For one of our young adult members in particular, this could be life-changing. He has difficulty attending educational establishments due to pain caused by artificial light.

Wider impacts: EPP often has considerable effects on future prospects of affected patients. Learning can have to be curtailed, and career options limited.

> *"My son is doing incredibly well and will be graduating next month from college with his degree in physics! This would not be possible were it not for the protective, life changing effects of Afamelanotide. Two years ago we feared for our son's life as he was in such a dark place due to the cruel and painful effects of EPP. At that time, he was on academic probation and had to go on meds to control his anxiety. Today, he is a happy, healthy and vibrant member of the student body at his college…"*

Another illustrative example is a young adult member who had to give up part-time employment in a cafeteria after the building was modernised with a design that included large expanses of mirrored walls. For this person the light in that building has become intolerable to bear for any length of time – the value that Afamelanotide could bring to such a case is immeasurable.

It is not only the quality of life benefits of the patients themselves which improve. Reports from family members makes it clear that they also suffer when their parent, child or sibling has EPP. For instance, the activities a family undertakes are curtailed by what the EPP patient can withstand. Their pain is also shared with loved ones. The draft recommendations do not fully take into account the costs and impact of this extended impaired quality of life.

Hidden costs of EPP: Discussion with our membership has uncovered how the costs of EPP can be hidden. The committee recognised that, even across the medical profession, awareness of EPP remains low (para 4.4). The evaluation also recognises that there is presently no truly effective and practicable treatment (para 4.2) and that EPP has a severe impact on patient lives (para 4.3).

What we feel is missing from the evaluation and associated studies is the existing underlying cost of EPP to patients and the nation. With no effective treatment available, many patients make little ongoing demand on NHS resources. This leads to an under-reporting of EPP episodes as well as a poor understanding of EPP in general. Moreover, despite severe psychological impact there is little or no recognised need, or funded, psychological and mental support for patients. Many simply suffer in silence sparing the NHS significant expense that does not appear in calculations. What psychological support is given is rarely ascribed to EPP. Were these 'true costs' being carried by the NHS at present ascribed accurately to EPP, then the cost per QALY would be lower.

We call for this deficiency in data to be acknowledged and for analysis models to be improved before a final recommendation is made. Ongoing improved understanding of a disorder calls for the improvement of existing approaches and the adoption of new ones.

2. Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?

No, we believe that the summaries and the criteria used in the recommendations fail to adequately take into account the difficulties in measuring EPP.

Problems with measurement

The formal trials had as a measure, the extent of sun exposure. While this is currently the only utilised measure, it has considerable limitations.

- EPP patients have, over a lifetime, developed a fear of exposure to bright light for any length of time. This behaviour is very hard to unlearn, and takes time.
- Patients were not told if they were on the treatment or the placebo, so many would be likely to still be very cautious.
- During the trials, there will have been cloudy days or days when other commitments prevented exposure, when they will have recorded zero sun exposure. This is in spite of the knowledge that EPP patients can be strongly affected even on cloudy days.

Other difficulties in attempting to measure EPP in the trials include:

- In EPP there are usually no visible signs – only reported symptoms – which means results are susceptible to highly variable individual factors.
- Seasonal impact of the trials: pain scores tend to be relatively low at the start of trials due to starting in the spring, so the full magnitude of the effectiveness of the drug might be difficult to track.
- Current methodologies cannot capture the value of any increased time in light.

Interpreting the evidence

The draft recommendations note that the committee themselves were concerned (para 4.20) that the ERG's own measures 'were highly uncertain because the benefits of Afamelanotide may not have been fully captured by the DLQI measured in the clinical trials'. Therefore the resulting QALY calculations cannot be seen as reliable or reasonable interpretations of the evidence.

3. 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?

No. There are some good points within the document and we are encouraged that NICE notes the severity of the condition and the far-reaching impact it has on the lives of EPP patients and their families (para 4.3). We are also pleased that NICE recognises that EPP was, until recently, a little understood condition (para 4.4). Nonetheless, we feel that the extreme extent and burden of the impact has still to be fully comprehended.

We fully appreciate the need for rigorous data and outcomes that can be used in fair comparison against other treatments on the grounds of health economics. We also understand how the conclusion has been derived. Despite this, we feel that the huge gulf in levels of impact between the data as applied in the QALY and the testimonies reported by EPP patients treated with Afamelanotide are too wide to be ignored. The patient reports are backed up by significant differences observed in these patients by recognised clinical experts in EPP. We feel that the

qualitative evidence must be taken more seriously until appropriate measurement tools can be designed.

4. 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?

We are concerned that until the dichotomy between patient and study data is fully addressed, and a more suitable method for assessing Afamelanotide is recognised by the committee, patients will be disadvantaged by the application of an evaluation model that does not permit true measurement of the level of suffering our members are subject to and the beneficial effects Afamelanotide has on lives of EPP patients.

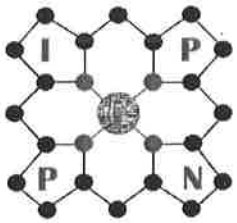
The BPA also considers that without full and proper consideration of the contentious issues that remain, our patients will continue to suffer from lack of economic opportunity and social isolation, that access to an effective treatment would counteract.

Our recommendations

1. That on further consideration NICE recommend Afamelanotide.
2. That if the final recommendation is not to approve, this should only be put forward once a consensus can be reached by the range of stakeholders on the methodology that should be applied to measure Afamelanotide's impact on quality of life.
3. That the statement relating to the review date is amended to '3 years, or sooner if significant evidence on the efficacy of Afamelanotide becomes available'.

References

[1] Biolcati, G., Marchesini, E., Sorge, F., Barbieri, L., Schneider-Yin, X. and Minder, E.I. Long-term observational study of Afamelanotide in 115 patients with erythropoietic protoporphyria. *British Journal of Dermatology.* 2015; 172(6): 1601-1612. Available at: https://dx.doi.org/10.1111/bjd.13598.



22 January 2018

Dear Dr Jackson, Ms Ekeledo, NICE Project Team members and HST Evaluation Committee members,

With this document the International Porphyria Patient Network (IPPN) provide their comments to the consultation "Afamelanotide for treating erythropoietic protoporphyria [ID927]", based on the public material made available by NICE through the following link:

www.nice.org.uk/guidance/indevelopment/gid-hst10009/consultation/html-content

As a general comment, the IPPN finds a significant inconsistency between the recognition by NICE that there is a "dichotomy between patient and clinical expert testimony and trial outcomes [sic]" and the fact that NICE insisted on evaluating the afamelanotide treatment by generic assessment methods rather than appropriately taking into consideration the uniqueness of erythropoietic protoporphyria (EPP) and the afamelanotide treatment effect. Regrettably, the challenges of assessing the consequences of EPP on patient lives and the efficacy of afamelanotide to manage the condition are largely neglected and NICE's evaluation methods are in stark contrast to those applied by other authorities such as the European Medicines Agency (EMA), who recognised that there are no tools and instruments allowing for a precise measurement of the impact of the disease and the benefit of the afamelanotide therapy[1]. Nonetheless, EMA accepted the positive trends from various clinical trials, the unanimous favourable reports of clinical experts and the testimonies of patients on the benefits of the medicine, and approved afamelanotide under "exceptional circumstances" for treatment of adult patients affected by EPP in 2014[1]. In addition and despite the acknowledgement that EPP is a disease that can have far reaching consequences on the lives of impacted people, NICE essentially minimised and overrode testimonies of EPP patients, as well as reports of clinical experts who describe the treatment as "transformative [sic]" and as a "dramatic step-change [sic]" in the management of this disease.

Specifically, the IPPN position on the 4 points, which the evaluation committee is interested in receiving comments on, is as follows:

1. Has all of the relevant evidence been taken into account?
   IPPN response: No – The overwhelming evidence from EPP sufferers, who have been under the afamelanotide treatment during the clinical trials or have access to the treatment in other countries and who experienced a dramatic change in the quality of their lives and in their health, has not been taken into account. In Italy, Switzerland, the Netherlands, Germany and Austria more than 200 patients have received afamelanotide, some of them for over 10 years, reporting dramatic benefits from the therapy.
2. Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?

IPPN response: No – EPP is a unique condition and any attempt to measure the efficacy of the afamelanotide treatment using generic methods does not fairly take into consideration the uniqueness of the condition; EMA, for example, clearly stated that the efficacy of afamelanotide could not be precisely quantified but approved the treatment because of the positive and significant trends from various clinical trials, and because there was clear evidence of clinical benefit reported by patients and healthcare professionals, who consistently reported improvements to patients' quality of life.

3. 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?
   IPPN response: No – As stated above the patients' experience of the significant limitations caused by EPP and the dramatic improvement of quality of life experienced by treated patients, also reported by their expert clinicians and emerging from the various clinical trials, have not been given sufficient credit and attention; we regard the quantitative assumptions leading to the recommendations given by the evaluation committee regrettably inadequate since the quantification methods applied are not appropriate in measuring treatment effects in EPP.
4. 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?
   IPPN response: Sadly, the urgent medical needs of most patients affected by ultra-rare diseases remain unmet. Only a small fraction of ultra-rare disease patients can benefit from effective therapies and EPP patients belong to this fraction of patients, with afamelanotide being the only existing therapy able to manage their disease. We now find that the committee is discriminating against British EPP patients compared to other EPP patients in Europe, who have access to this medicine because it was assessed by recognising the unique nature of the disease and by taking into account patient experience and expert clinician input; the committee unfortunately remains resolute against assessing afamelanotide with the uniqueness of the condition taken into appropriate consideration. The discrimination also occurs by not considering adequate – potentially new if needed – assessment methods which allow evaluating the effectiveness of afamelanotide. Thus, a discrimination occurs in comparison to other patients in general but also to patients who suffer from other ultra-orphan conditions. Equitable medicine access for all British patients, whether the condition is rare or common, is a fundamental principle of the National Health Service. We find that the committee's recommendation could compromise this principle.

In the table below, starting on page 4, please find a more detailed response, with comments addressing the four questions above and specific sections of the "Evaluation consultation document" (IPPN Response to "Evaluation consultation document").

At the end of this section, on page 3, please also find a description of the unique features of EPP (About the uniqueness of EPP).

We trust that our comments, corrections and recommendations will be helpful to NICE and will be taken into consideration to produce a final guidance that is aligned with the urgent unmet medical needs of EPP patients in the United Kingdom, restores their health and dignity, gives them the opportunity to live a more normal life, treats them equitably and does not discriminate against them compared to other EPP patients in Europe, who have access to the afamelanotide therapy because it was assessed by recognising the unique nature of their disease, and to other patients in general.

We urge the committee to take our concerns seriously and to revisit their recommendation based on the considerable evidence presented and by applying appraisal measures in line with the peculiarities of EPP.

With best regards,

[redacted] on behalf of IPPN
[redacted] of the International Porphyria Patient Network, and [redacted]
[redacted] of the Swiss Society for Porphyria

About the uniqueness of EPP

EPP is unique in that it features a collection of manifestations and conditions which represent a significant clinical challenge to effectively, objectively and conclusively assess disease impact and management. The following is a list of key features which illustrate the uniqueness of EPP:

- The endogenously occurring phototoxic reactions
- The related excruciating neuropathic pain which cannot be managed by any medication
- The extreme fatigue developing after even relatively mild phototoxic reactions which negatively impacts productivity and, in addition to the severe pain, completely incapacitates patients when the phototoxic reaction is protracted and/or more intense
- The debilitating, disfiguring, professionally and socially disabling nature of the disease
- The significantly variable environmental conditions which can trigger phototoxic reactions in highly unpredictable fashion (direct light, light through clouds, light reflected from surfaces such as buildings, windows, water, snow, fog and clouds; seasonal cycles and weather conditions, including wind with its considerable negative impact; differences in geographical latitude; etc.)
- The absence of accessible and measurable biochemical or other clinical features to objectively assess the magnitude and duration of phototoxic reactions, and consequently the lack of efficacy biomarkers to measure the effect of therapeutic interventions
- The mostly invisible nature of the phototoxic reactions, with EPP sufferers being in extreme pain without any apparent external cutaneous signs except when reactions are particularly violent and protracted
- The invisibility of EPP leads to a lack of understanding from others, even allegations of malingering, and as a result patients frequently decide to hide and downplay their condition, suffering in silence and alone
- And finally, the traumatic experience of phototoxic reactions, particularly during childhood, leads to a deeply ingrained fear of light and of its incapacitating consequences which accompanies sufferers and conditions their behaviour during their entire lifetime, forcing them into an existence of light deprivation with all its physical and mental health consequences

With all these variables it is evident that measuring the impact of EPP and the effectiveness of any therapy to manage this disease is a daunting task which cannot be addressed using generic assessment tools and requires a more adaptable, innovative, disease-specific and patient-centric approach, an approach that in our opinion has not been adopted in NICE's appraisal of afamelanotide for treating EPP.

IPPN Response to "Evaluation consultation document" (literature references at the end of the table)

Section	Citation from document	IPPN response
1.2(a)	Afamelanotide works by increasing melanin in the skin, which makes the skin tan, giving some protection against light damage.	In addition it should be mentioned that afamelanotide has both an anti-inflammatory and anti-oxidative activity, which likely contribute significantly to its effectiveness in EPP[2-4].
1.2(b)	Clinical trial results suggest that afamelanotide may be effective. But it's unclear how effective it is, whether the effectiveness varies from person to person and how it affects quality of life.	This statement is inaccurate: In the 2015 Biolcati et al. observational study[5], it has been shown that only 2.6% of EPP patients treated with afamelanotide have described lack of effectiveness of the therapy in improving their symptoms, while 97.4% of them benefited from the afamelanotide treatment (i.e., 112 of the 115 patients in the study). We interviewed Prof Dr Elisabeth Minder, co-author of the study and director of the National Reference Centre for Porphyrias at the Triemli City Hospital in Zurich, Switzerland; she states: "Our clinical experience treating EPP patients covers more than 30 years, during which we tried every potentially effective therapy for EPP, and they all proved to be inefficacious except for afamelanotide. During the last 12 years we applied afamelanotide to a total of 83 different patients. The very few patients who did not benefit from afamelanotide, stopped treatment after the first dose, i.e., even if afamelanotide is available to them they discontinue treatment, causing no additional ineffective use of resources to our Swiss healthcare system. On the other hand, the extremely high treatment adherence in the great majority of patients, as also highlighted by Biolcati et al.[5], underscores the effectiveness of afamelanotide in improving patient lives. Our clinical experience shows afamelanotide to substantially improve physical and mental health, and quality of life for patients. Those who are moderately affected by EPP can lead a normal to nearly normal life under the treatment, and patients who are more severely affected by EPP experience a significant improvement in quality of life after they receive afamelanotide. Patients consistently call the medicine "life-changing", a "wonder medicine", and they report of a continuous, sustained improvement in their health and lives over time. They could not image going back to the life they had before without the treatment. Unfortunately, some of them did have to experience this as their treatment was interrupted in the year 2016, when we had to re-negotiate reimbursement with Swiss health insurances for every individual of the total 33 Swiss residents we are treating (in addition to Swiss patients we also treat individuals from other nations, including the USA, who regularly travel to Zurich to receive the treatment). This was a very challenging period which was however extremely revealing in pointing out how afamelanotide is essential for patients. For example and as an illustration of the gravity of the situation, as a consequence of light deprivation and the painful phototoxic reactions resulting from treatment interruption one patient required hospitalisation because of exacerbated depression; several other patients showed signs of depression and had suicidal thoughts; and two patients had to quit their jobs because working conditions exposed them to sunlight and in the absence of treatment they were

		subject to phototoxic reactions again as opposed to when they were under treatment. Now fortunately, we could successfully re-negotiate reimbursement and patients receive the treatment again and are back to their normal, productive new lives." Additionally, the European Medicines Agency (EMA) summarise the results for all Phase III clinical trials and the second Phase II trial as significant, with verum patients able to spend more time in direct sunlight, and experiencing both less phototoxic episodes and lower maximum pain severity per phototoxic episode (see table on pages 74-75 in the EPAR report[1]). From this collective evidence we conclude that the afamelanotide treatment **is clearly** and significantly effective and of benefit to EPP patients, and do not agree with the committee's assessment that the treatment **may be** effective and that it is **unclear** how effective it is.
1.2(c), 4.10, 4.14	1.2: The cost-effectiveness estimates for afamelanotide are all much higher than the range normally considered acceptable for highly specialised technologies. This is despite taking account of the impact on quality of life, 'disability', and likely non-health-related benefits such as improving employment and study options, and that afamelanotide is an innovative treatment. 4.10: The committee discussed the DLQI. It was aware that this is a validated quality-of-life questionnaire, but validated for conditions only affecting the skin, rather than for EPP. The committee noted that the ERG considered that, although not perfect, the DLQI addresses some factors that impact on the quality of life of a person with EPP, such as pain and ability to work or study.	The cost-effectiveness calculations applied by NICE's evidence review group (ERG) are based on misleading assumptions, in particular as it relates to adoption of the DLQI, which they have used in their calculations. We outline below why the use of the DLQI as basis of a quality of life (QoL) determination in EPP is inappropriate: 1. At least 2 of the 10 questions of the DLQI do not apply to EPP (Q 9&10), which reduces responsiveness/sensitivity. 2. The wording of the DLQI questions does not adequately describe EPP-related symptoms, which leads to uncertainty and irreproducibility in the answers given by EPP patients. 3. The responsiveness/sensitivity of the DLQI has never been validated for the efficacy assessment of a treatment for EPP. The limitations of health status (HS) scores have been elaborated by Hamming & De Vries[6]: They highlight that the World Health Organisation (WHO) working group has defined QoL as "the concept with emphasis on the personal evaluation of functioning in relation to individual and/or cultural standards, values, expectations and goals[7]". Therefore, the perception of disease and treatment should not only be recorded (e.g., by measuring HS scores), but also evaluated by the patient, as Hamming & De Vries conclude: "A true assessment of the impact of illness and the outcome of a treatment can be made only if the perception of the patient as an individual is evaluated properly[6]." This did not occur with the DLQI, a generic tool for dermatological conditions which should never be applied to EPP since EPP is not a dermatological disease. Instead, Biolcati et al.[5] performed a direct evaluation of the afamelanotide treatment effects using the Swiss version of the EPP-QoL questionnaire, an EPP-specific tool, in line with the recommendations of Hamming & De Vries[6]. The patients scored their quality of life directly on a Likert-type scale by answering the question: "Taking your EPP into account, mark the box which best describes the quality of life 'NOW', whereby 0 means the worst possible and 10 the best possible life quality" (Appendix 1 in Biolcati et al.[5]). The outcome of this direct QoL evaluation was the following: The current life quality in untreated and treated adult EPP patients resulted in scores of ***4.0 ± 2.9 and 8.0 ± 1.9**, respectively, **with the difference having a statistically high significance (P < 0.001)*** (Biolcati et al.[5]). This direct evaluation of

	4.14: The committee therefore considered that the ERG's approach may have underestimated the real-life benefits of afamelanotide because these may potentially have been underestimated in the trials, but that it was not possible to quantify by how much. It concluded that the ERG's exploratory modelling approach was its preferred approach.	the effects of the afamelanotide treatment on personal QoL reflects the highly significant improvement of the perceived general health and life quality reported by EPP patients over a period of 8 years, a considerable timescale and a reality that unfortunately cannot be captured by generic tools such as the DLQI, ineffective and inadequate in EPP. As we do not possess any expertise in health economics, we do not feel we can make any informed comments on the models used for the cost-effectiveness estimates. However, it is apparent that in these models the ERG did not take into account statements by expert clinicians and patients on the transformative and life-changing properties of the afamelanotide treatment (captured in detail in the full Evaluation Report [committee papers][8]), nor real world evidence such as that reported by Biolcati et al.[5]. In fact, the ERG completely minimise and override this important input which translates effectively the abstract improvements emerging from the clinical trials to the actual clinical benefit experienced by patients. The ERG has not adequately taken into consideration the challenges which typically characterise clinical trials for rare diseases; they override the assessment made by the EMA which recognise that "Under normal conditions of use, the status of current scientific knowledge, tools and instruments, does not allow for sufficient precise measurements of impact of disease" (page 90 in the EPAR report[1]), and despite this conclusion the ERG insist on applying generic assessment methods clearly inappropriate in EPP; and finally the ERG largely neglects the positive outcomes and trends that, in spite of all the challenges, do emerge from the clinical trials (e.g., see table on pages 74-75 in the EPAR report[1]). We therefore urge NICE to ensure that a balanced approach be applied to the cost-effectiveness estimates, taking all inputs, trends and limitations into consideration which, it must be stressed, other European national authorities and the EMA have used to decide in order to make afamelanotide available to European EPP patients. As example, we refer here to the comprehensive evaluation carried out by the German Institute for Quality and Efficiency in Healthcare (IQWiG), the German Federal Joint Committee (G-BA) and an Arbitration Board called under the German Pharmaceuticals Market Reorganisation Act (AMNOG)[9], after which a pricing agreement was reached and a reimbursement amount binding for all German state health insurers was set[10]. This outcome was obtained after the German authorities took into account and reviewed all the data and information. This is a process which aims to find a cost-effective solution for all involved stakeholders and takes into objective consideration both the costs of innovative therapies and the long-term sustainability of medicine access to patients. In the case of afamelanotide there has been an evident agreement that all conditions were met to ensure access to German patients.
2.1(a)	Erythropoietic protoporphyria (EPP) is a genetic storage disorder.	EPP is not a "storage disorder". EPP is an inborn error of metabolism leading to accumulation of protoporphyrin IX.
2.1(b)	This causes phototoxicity (a	We recommend extending this description as follows: This causes phototoxicity (a chemical reaction in the skin with destruction of

	chemical reaction in the skin), and the skin may become painful, swollen, itchy and red.	subpapillary capillaries and perifocal edema), and the skin becomes painful, swollen, itchy and red, and in more severe episodes petechias and skin erosions occur.
4.2	Clinical experts stated that beta carotene and narrow band UVB therapy have been tried as treatments to prevent phototoxicity but these are decreasingly used because of lack of clinical effectiveness.	Beside their lack of effectiveness in EPP, beta carotene has been associated with increased risk of death from lung cancer and cardiovascular disease[11], and UVB exposure is well known to increase risk of developing skin cancer with a delayed incidence of several years. These are additional factors discouraging such treatments whose life-long administration would expose EPP patients to considerable risks to their health.
4.5	The committee concluded that there is some variation in how long people with EPP can be exposed to sunlight without a reaction, but the range across people diagnosed with EPP in England, and any variation in patient experience of the condition, was unclear because of a lack of data.	This is inaccurate since Holme et al.[12] have published data for EPP patients in the U.K. According to this paper the median time for onset of symptoms following exposure to sunlight was 20 min (lower quartile: 10 min; upper quartile: 60 min; range: immediately to 12 h or asymptomatic). We also want to point out that, despite some individual variance in the time it takes for a phototoxic reaction to occur, it is often too late to realise that a severe reaction is underway. The given circumstances might also prevent patients from seeking shelter from additional phototoxic exposure which precipitates a reaction very rapidly, and then the resulting consequences (severe pain, fatigue, incapacitation, etc.) are very similar across patients.
4.7(a)	However, the committee also heard that, in the long-term observational study (Biolcati et al. 2015), there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials.	In the clinical experience of the National Reference Centre for Porphyria in Zurich, Switzerland, led by Prof Dr Elisabeth Minder, co-author of the Biolcati et al. paper[5], the improvement of the QoL markedly precedes the change in life style. Patients require at least 2-3 years of continuous treatment with afamelanotide until they report a decrease in their fear of light and until they start changing their lives in a positive way, such as by switching to new, typically better compensated employment which might subject them to increased light exposure. Also, we consider the QoL score of about 80% as the maximum score typically achieved in any QoL questionnaire, so that a further increase cannot be expected.
4.7(b)	The committee concluded that the trials had shown relatively small benefits with afamelanotide, that even small benefits are important to patients, and that clinical and patient experts believed the effects would be greater than that seen	We reiterate that the real life benefit of the treatment is dramatically more substantial than what may appear from the clinical trials. As key study we refer here to the Biolcati et al. paper[5], where afamelanotide was applied under routine outpatient clinical conditions over several years, the response rate was 97% and treatment adherence exceptionally high. In addition, there is ample anecdotal evidence from patients beyond those investigated by Biolcati et al.[5] that the benefits of afamelanotide are life-altering and dramatic.

	in the trials.	
4.8	The committee concluded that there was a substantial dichotomy between patient and clinical expert testimony and trial outcomes, and the true extent of benefit was unclear.	This is a key issue: The clinical trials measured spontaneous sunlight exposure and not light tolerance, which are often confused. In the data evaluation of the clinical trials the average daily increase in sunlight exposure has been diluted by rainy or cloudy days, or by days during which patients could not expose themselves to sunlight because they were either working indoors or otherwise busy with indoor occupations. Evidently, during those days no sunlight exposure was reported in the diaries used in the clinical trials. This resulted in a statistically significant but small absolute increase of time in sunlight. Such outcome leads to the erroneous perception that the clinical benefit of afamelanotide in EPP is limited. Moreover, there is no effective comparator as we do not know the average daily time of sunlight exposure of a normal population. Taking the widespread vitamin D deficiency in a normal population into account, which could be alleviated by only 15 min sunlight exposure per day, we can extrapolate that the daily average spontaneous sunlight exposure in a normal U.K. population ranges in the minutes and certainly not hours. Unfortunately, we could not find any conclusive scientific data about this. Nonetheless, with this assumption an average gain of 8 min per day (page 102 in the EPAR report[1]) has to be considered as a substantial improvement.
4.9(a)	The committee discussed how quality of life had been assessed in the clinical trials. It noted that the generic short-form 36 (SF-36) and generic skin condition Dermatology Life Quality Index (DLQI) had been used in some of the clinical trials. However, the company stated that it had received advice that these measures were not appropriate for capturing the quality of life of people with EPP.	The responsiveness of generic questionnaires such as the SF-36 and the DLQI on treatment effects have not been scientifically assessed in EPP and are therefore not suitable. We reject these questionnaires as tools to measure quality of life in EPP patients since they have not been validated for EPP. Biolcati et al.[5] have developed a psychometrically validated EPP-QoL questionnaire with the support of an independent expert commercial provider (Oxford Outcomes). This EPP-QoL questionnaire is described as appropriate by patients and it is significantly superior to the generic SF-36 and DLQI questionnaires. Moreover, the latter was validated for dermatological conditions. EPP is not a dermatological condition, despite its cutaneous manifestations, and features completely different characteristics that need to be taken into consideration when measuring quality of life in EPP patients. EMA's EPAR report also notes the non-specific nature of the DLQI in EPP: "The Dermatology Life Quality Index (DLQI) was employed. This is a questionnaire not specific for EPP patients but widely used in dermatology for QoL assessment (e.g. in vitiligo, psoriasis, and atopic dermatitis) (page 90[1])." Here, it is important to refer once more to Hamming & De Vries[6] who recommend that patients need to evaluate a treatment rather than just measuring health status as in these generic questionnaires. Not doing so, might result in misleading and inaccurate results such as when the DLQI is applied to EPP. Along the same lines EURORDIS, the European alliance of rare disease patient organisations, in its concept paper from the 23rd Workshop of the EURORDIS Round Table of Companies comment on the relevance of individual patient input: "Patient-Reported Outcomes are one way of obtaining such results. Those are measurements based on data provided by patients (self-report or interview) regarding their health condition

		without amendment or interpretation of the patient's response by a clinician or anyone else[13]." And finally, EMA themselves have recommended that individual case descriptions be used as evidence: "Overall the experts and patients consulted during the ad hoc meeting considered that additional evidence through individual case description has its value and should be taken into account in particular for EPP. The CHMP agreed with the experts, clinicians and patients and were reasonably convinced of the trial data showing an effect of Scenesse (page 102 in the EPAR report[1])."
4.9(b)	The committee further noted that the company had developed a condition-specific quality-of-life questionnaire. Furthermore, the EPP-QoL had been modified while the trials were ongoing and data were being collected, and some questions were removed.	First, the statement "the company had developed a condition-specific quality-of-life questionnaire" is inexact: The EPP-QoL was not developed by the company alone but in collaboration with the expert clinicians who authored the Biolcati et al. paper[5] and who used patient input to appropriately formulate the questions. Second, the modification of the questionnaire "while data were being collected" is not relevant because as demonstrated by Biolcati et al.[5] the removal of the questions from the first version of the EPP-QoL questionnaire did not affect the results of its final version: "During subsequent psychometric validation by Oxford Outcomes (Oxford, U.K.), a further three questions were removed (No. 3, 12 and 16). The scores were corrected for missing values by multiplying the sum of the answers by the factor: total possible answers/number of answers[5]." Third, we want to reiterate the fact that the committee should have taken into consideration the inherent challenges of studying such an ultra-rare disease as EPP, a condition calling for increased regulatory adaptability and nimbleness. At the outset of the clinical trials very little was known about this condition and there were near to no extensive scientific observational studies of patient behaviours and disease impact. We as EPP and porphyria patient community, advocates and clinicians learned about the disease as we went through the trials and initial assumptions had to be amended during the process. It would have been inappropriate not to amend such assumptions as we learned more about the disease, e.g., by not removing inadequate questions from the evolving EPP-QoL questionnaire. This approach is also captured in the EPAR report as a normal element of the validation process: "The Applicant got the EPP-QoL revised by a CRO. The CRO were not able to fully validate the questionnaire but did review the scoring algorithm. Changes were suggested to the original EPP-QoL (e.g. omission of questions) (page 64[1])." While the CRO was not able to "fully validate" the questionnaire, we regard a "semi-validation" far superior to a "non-validation" like for the SF-36 and DLQI with regards to EPP. Again, the generic SF-36 and DLQI questionnaires should not be applied to EPP and the latter was validated for dermatological conditions and EPP, despite its cutaneous manifestations, is not a dermatological condition.
4.9(c)	The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that	We strongly disagree with this statement: In our experience, the EPP-QoL was the only questionnaire that patients ever considered adequate to capture the symptoms and limitations of their disease. The National Reference Centre for Porphyria in Zurich, Switzerland, led by Prof Dr Elisabeth Minder has a substantial amount of data on

	people with the condition and their clinicians report as important. It also concluded that, without appropriate validation, there was substantial uncertainty about how the EPP-QoL could be interpreted and whether it would reliably capture any treatment benefits with afamelanotide.	this, in addition to those used in the Biolcati et al. paper[5]. Full evaluation and publication of the data is pending but the evidence and patient testimonies clearly point to the EPP-QoL being significantly more appropriate than the DLQI. Moreover, we want to make the committee aware of the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which have been adopted by the EMA: "If quality of life is measured, it should always be assessed using scales validated for the particular indication being treated. It is recognised that sometimes there are too few patients for validation exercises as well as separate treatment evaluation[14]." Unfortunately, the committee is not sufficiently taking into consideration a fact that is otherwise accepted by other relevant authorities: EPP is an ultra-rare condition with very low numbers of patients, and this disease and any treatment to address it cannot be adequately measured with generic tools. A disease-specific approach taking into account patient input has to be considered even if its full validation might not be feasible. Not doing so is a discrimination against EPP patients which we find extremely concerning. Other European EPP patient communities have not experienced this discrimination and have access to afamelanotide because their authorities recognised the uniqueness of their condition and applied adequate assessment methods.
4.11	The committee considered the validity of the EPP-QoL to be highly uncertain (see section 4.9) and concluded that the company's arbitrary approach to stratifying disease severity added to this uncertainty.	See our comments to section 4.9
4.3, 4.20	4.3: The committee concluded that EPP can have a far reaching impact on the lives of patients and their families, resulting in anxiety, social isolation and very poor quality of life. 4.20: The committee acknowledged that EPP, although not life threatening, can cause extreme pain, be very debilitating and have far reaching consequences on living a normal life. It was aware that even small increases in time	We agree with the committee's assessment of the severe impact of EPP on patient lives and that afamelanotide is the only treatment which has shown efficacy in preventing phototoxicity in EPP. We want to add that afamelanotide also decreases the severity of phototoxic reactions and the duration of recovery after a phototoxic reaction (see also table on pages 74-75 in the EPAR report[1]), two aspects to which little attention has been given by the committee. These two aspects are however of utmost relevance to patients who have or have had experience with the afamelanotide treatment as they are invariably reported to contribute significantly to the value of the treatment. These aspects have to be taken into consideration in the benefit assessment of afamelanotide in EPP and the related cost-effectiveness estimates. In addition and as a conclusion, we want to point out the contradiction between the statement in section 4.20 that "even small increases in time spent under light could significantly improve people's lives" and the committee's negative recommendation against afamelanotide for treating EPP. We are disconcerted about this contradiction and concerned about the negative recommendation

	spent under light could significantly improve people's lives. It noted that afamelanotide is the only treatment for preventing phototoxicity in EPP for which efficacy has been shown.	despite all the evidence, patient testimonies and expert clinician input about afamelanotide effectively addressing patient needs and enabling them to not only gain a "small increase in time spent under light", which would already "significantly improve people's lives", but in reality to dramatically increase the time they can spend under light. We urge the committee to take our concerns seriously and to revisit their recommendation by applying appraisal measures in line with the peculiarities of EPP and with the considerable evidence presented.

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British Association of Dermatologists
Response to NICE Highly Specialised Technology Appraisal
Evaluation Consultation Document:
Afamelanotide for treating erythropoietic protoporphyria [ID927]

On behalf of the British Association of Dermatologists (BAD), thank you for the opportunity to comment on this Evaluation Consultation Document.

Has all of the relevant evidence been taken into account?
The expert and patient testimony has a prominent role in the evaluation of this treatment. That testimony has been taken into account in terms of the panel's response as human beings to the physicians and patients, but not for the evaluation of cost effectiveness. We acknowledge that this is difficult, and realise it may be challenging to do technically. However, we feel that if one did/could quantify "testimony" or "non-clinical trial data" (since the testimony shows such a dramatically greater efficacy than the trial data), it would result in a cost/QALY that would be fundable by NICE.

We also think that part of the problem is that the trials picked up *some* of the efficacy but not all of it, which has led to the high cost/QALY. We note that patient and physician testimony played a significant role in being considered along with the trial data, in decisions concerning the licensing of this drug. We are aware that the situation with considerations of funding may be different from those faced by a licensing body but wonder if the expert team at NICE can think of a way of factoring this in.

It is perhaps not surprising that the clinical trials have picked up a therapeutic effect, but not the full dramatic therapeutic effect, which was reported by patients and their physicians, to the NICE committee. The obstacles in conducting these trials were huge, both because of the challenges of dealing with a rare disease, and the difficulties regarding the measures and metrics used as endpoints.

A further major challenge, that was not discussed at the NICE meeting, is the influence that seasonality of EPP has on its impact on quality of life and clinical scoring within clinical trials. As trials plan a springtime start (before patients face their major sunlight challenges, and so that patients are treated across the summer months) patients enter the trials with a low baseline clinical score and low impact on QoL as their condition is less severe at that time, with a seasonal worsening of scores during the trial as they go into the summer. Although the trials are randomised and controlled, this seasonal variation in severity is likely to undermine the full assessment of efficacy.

There is also further evidence relevant to the DLQI to take into account. At the meeting there was much discussion, and questioning of a clinical expert, as to the potential reasons for the difference between the DLQI findings in the Holme *et al. Br J Dermatol* 2006 study (high DLQI score) and the EPP clinical trial in the *New Engl J Med* 2015 (lower baseline score). The clinical expert has examined the Holme paper subsequently and found an important aspect of the methodology was missing from the paper; she has personally contacted the paper's senior author who had also noted the omission, and provided the information that the DLQI was collected (by the junior researcher on personally visiting the patients) over the spring and summer months, i.e. predominantly when the patients would be most affected. This contrasts with the EPP clinical trials, where the treatment was aimed to start before the patients developed seasonal worsening.

Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?
Please see the response above.

Are the provisional recommendations sound and a suitable basis for guidance to NHS England?
We think the provisional recommendation is the wrong decision for patients with EPP. It is a deeply frustrating one and a deeply frustrating situation, for the patients, and physicians. If NICE could find a way of including/quantifying testimony from patients and physicians in the cost effectiveness calculation in some way, and potentially of quantifying the impact of the many unique confounding factors affecting assessment of this disorder, this would be invaluable.

If the funding cannot be made available in the 'classical' way, we request that consideration should be given to creating a 'managed access scheme' or similar. People with EPP could be treated during an agreed assessment period (e.g. at least 2 consecutive years) for further data collection. This could potentially be done in specialised centres in Manchester (Salford Royal) and London (Guy's & St Thomas') which would also aim to help people with EPP alter their behaviour – "unlearning" a lifetime of avoiding the outdoors due to the severe pain endured), one of the factors that has probably contributed to the mismatch between the trial data and the patient testimony.

The further data collection would focus on the lessons learned from the trials in order to collect information that more fully captures therapeutic effects by taking into account the following considerations:

- additional seasonality consideration makes it challenging to capture the full benefit of treatment using generic assessment tools, especially combined with the significant others that were discussed at the meeting, including the need for a specific assessment tool for this complex skin/metabolic/apprehension-avoidance condition that appropriately encompasses the pivotal impact of sunlight
- small differences in ability to tolerate sunlight exposure making major differences to patients
- understandable hesitancy in sunlight exposure during limited duration trials due to learned behaviour following experience of earlier severe pain attacks, and time taken to adapt.

Additional comments:
There are issues around the assessment of orphan/rare diseases by standard scoring and costing models and perhaps these have contributed to the problem. Is there more scope to factor in a multi-dimensional assessment of such conditions, where it was understood that they may not always fit standard models? We are aware that the measure used is cost effectiveness per patient. Nevertheless, we would like to make the obvious point that EPP is a rare condition, so that the total cost of treating all the EPP patients in the UK with afamelanotide would be relatively low.

[redacted]
On behalf of the BAD's Therapy & Guidelines sub-committee

Highly Specialised Technology

Afamelanotide for treating erythropoietic protoporphyria [ID927]

Evaluation consultation document

Stakeholder Organisations: Royal College of Pathologists/British Society for Haematology

Name of commenter: [redacted]

Has all of the relevant evidence been taken into account?

Yes; Due account has also been given of patient testimony, in addition to published clinical trial data.

Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

Yes, though it is noted that the company (Clinuvel) disagrees with some aspects of the assessment and modelling.

Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

Given current financial constraints and pressure on NHS funding, the recommendations appear to be sound and fair

I do not have anything further to add as the committee's assessment is extremely comprehensive and detailed.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	British Society for Haematology
Location	England
Conflict	n/a
Notes	The comments given are by [redacted] on behalf of the BSH.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Has all of the relevant evidence been taken into account? Yes; Due account has also been given of patient testimony, in addition to published clinical trial data. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence? Yes, though it is noted that the company (Clinuvel) disagrees with some aspects of the assessment and modelling. Are the provisional recommendations sound and a suitable basis for guidance to NHS England? Given current financial constraints and pressure on NHS funding, the recommendations appear to be sound and fair I do not have anything further to add as the committee's assessment is extremely comprehensive and detailed.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	What can I say about EPP. Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to switch on the TV or look at your phone because every time you do you feel like you are on fire. Imagine not being able to do your job because the office lights cause you pain. That is my day, every day, not just in the summer, but even in winter. Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. I took part in a clinical trial for afamelanotide. My life changed. I went out of the house in shorts and T Shirt, I sat in the sun, I had the best year of my life. I went from suffering to enjoyment in a couple of weeks! I could spend hours out in the sun without pain for the first time in my life. Now I'm back to hiding, avoiding things, I can't even take my children to school without wearing hat, coat and gloves. This treatment is life changing. I am psychologically damaged by this condition. I have suicidal thoughts because of the pain, and now my Children who are 3 and 6 are being damaged by this condition. Even though they don't have EPP they are scared to go out in the sun because it hurts Daddy. They should not be suffering just because I am. I am rapidly heading towards having to give up work due to EPP. Incandescent lightbulbs are no longer available to buy in the UK. Energy efficient bulbs, LED bulbs, Flourescent tubes

	and halogen bulbs all give off light in the spectrum that affects those of us with EPP. This means that wherever I go I am in pain, I struggle to use a laptop, a mobile phone, to watch TV all because of EPP. I sit at home some time, with the curtains closed, the lights off, the TV off, not even able to send a text message because the screen of my phone burns me. If EPP stops me working then the cost will be far greater than the cost of this drug. This is a pain that no pain killer can touch, a pain that no sun cream can prevent, a pain that leaves me permanently exhausted, but I carry on, because I have to carry on, for the sake of my sanity, for the sake of my marriage, and most of all for the sake of my children. I am bullied every day, I am laughed at and called names because I have to cover up. Can you try to picture driving a car in summer, wearing a coat, a hat and gloves. That is what I have to do, that is what I did to get here today. I have to ask people to turn lights off for me, to close curtains and blinds. Some days I will be in extreme pain but show no outward signs, no rash, no swelling, no tan. There is nothing wrong with me? I'm making it up? I wish I was. This drug is life changing, not just for me, not just for my family, not just for my employer but for everyone affected by EPP. If I had cancer you would give me Chemo. If I was addicted to heroin you would give me methadone. If I had a bad back you would give me pain killers. I have EPP. What do you give me? You have the power to stop this pain, to stop this hurt and to stop this mental torture. The power to give me a life.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have the misfortune to have been born with EPP. A rare genetic blood condition. This has and still does affect my whole life. I am laughed at, even by medical practioners, also with comments such as, “aren’t you hot dressed like that” when covered from head to toe with brilliant sunlight shining. Yes I am hot, but much better than suffering the excruciating pain when my skin is exposed to sunlight, indoor outdoor lights. I have had my hands scrubbed with a scrubbing brush by a dinner lady at the junior school I attended, because she wouldn’t believe the discolourisation on my hands was not dirt. If you can imagine the pain I was already in before her attack on me hot coals under my skin then add what she did. Excruciating does not come near to describing it. To feel as though your blood is literally boiling day and night for days and weeks after a few minutes exposure to light is torture. To then have to be confined to a dark room and a few seconds at a time of very slight relief when something soft and cool is applied. When as a child we were given Calomine Lotion to apply huh, a few seconds of relief followed by a magnified excruciating pain as the lotion quickly dried on my skin. Nothing I have ever tried has helped with the pain, no painkillers, no sunscreen. The only thing so far has been to wear protective clothing, hats, long sleeves, trousers, socks gloves shoes or boots. Pile the clothes on while others strip theirs off. The only time I can feel slightly normal is during the winter months when others cover up because of the cold, the giveaway that I am not normal is my hats and face coverings. I am so isolated and depressed because of EPP. Even family members do not fully understand what I go through, “come outside its cloudy now”, cloudy it may be but the sun’s rays still find their target, me. Visiting people is out of the question as they have no tinting on their windows so they do not understand why I would keep my coat, gloves, and hat on when in their houses. For many years I tried to be normal but I always cried alone at night keeping my pain to myself. Looking as though nothing is wrong with you doesn’t help as no one can imagine or believe

	how much pain I go through each and every day of my life. I have heard of the wonders of the implant, how those lucky enough to have taken part in the trials have had such fantastic times in the sunshine. This I can only dream of and long for. To be able to go out in the sunshine, to be able to go out without having to get dressed up as if going on an arctic adventure. Must I die without this dream becoming a reality for me and many many others suffering the same fate. I take vit D tablets daily as prescribed by my EPP specialist, this has only been for the last 5/6 years, as before I saw no one who could or would help with my EPP, I need to take a large amount as I protect myself from the sun to such an extent. Being anaemic as my body cannot absorb iron because of EPP, means I am tired most of the time as supplements would endanger me. My vit D levels have been so low an EPP specialist was amazed that I had not had any fits. Before the law was changed in the UK on window tinting I was able to go out and about driving all over the place as the tinting applied to the windows helped enormously plus my usual covering up. I even passed my advanced driving tests. I can no longer do that as having to have 75% of light coming into the drivers windows has put paid to that as I cannot go out so much because of the pain it causes.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Parent
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Before you decide not to go ahead with this drug for people who suffer from EPP I would like to tell you about my son who has EPP and has a daily struggle with it. My son is called [redacted] and has suffered all his life with EPP. He is the only family member with it. He is now 14 years old and still suffers from it. The thought of him receiving the drug at 18 keeps him going at times. He gets bullied at school through having EPP and has had phone calls from other lads his age threatening to burn him with torches and at the end of the day he just wants to be "normal". Here's a question for you, Have you ever seen your child in so much pain and all you can do is watch them suffer as a hug burns them more. My son burns inside out and the pain is written all over his face. The only thing that soothes his pain is by applying cold water and this might give him seconds of relief. He takes paracetamol and ibuprofen together with an antihistamine and this doesn't ease his pain. He burns for days at a time. When his hands are on fire I have to feed him, help toilet and wash him. When his feet burn I have to carry him as they are too painful to walk. When his lips are on fire he can't eat anything hot as this makes his lips burn even more. He has lived off ice pops and ice cream for days at a time. [redacted]'s lips split very deep leaving them scarred. His face swells up which adds to the discomfort he endures. He is always vitamin D deficit and takes vitamin D supplements every day. His body doesn't use iron properly so is always anaemic but cannot have iron supplements. He has become calcium deficit due to the vitamin D deficiency which leaves him having palpitations, bad stomach pains, bad nausea, dizziness and nearly being admitted to hospital. He has to be covered up constantly even in winter with protective clothing which consists of a hat, long sleeves tops and jackets, long legged pants, gloves and a face cover. He has people staring at him and talking about him. He has been accused of trying to rob the post office and asked which bank is he going to rob. He has been classed as a thug type with all his protection on. This upsets him greatly. I have to encourage him to go outside at times with his friends. He refuses to go on school trips abroad just in case he has a reaction as he doesn't want to spoil thing for the other school children. I have even

	signed his forms and he hasn't handed them in. He has started light therapy to try and build up his pigmentation and help him not have as many reactions. This causes him to have reactions at the beginning of the treatment. He has 15-18 sessions of this and it goes over a period of 5-6 weeks. [redacted] has blood test every 3 months to keep a check on his vitamin D levels. This affects our family greatly as we have to go on days out on cloudier days. We don't go to the beach in the summer with our two younger girls who don't have EPP as it gets too much for [redacted] in the heat. [redacted] is constantly tired due to the iron and has to have plenty of resting and cooling down times if we do go to an event in summer and have to plan for indoor activities as well. If we're going swimming [redacted] has to wear a full swimming suit which he wears if we get the paddling pool out and he goes in the pool in an evening or when the sun isn't at its hottest. We have never taken [redacted] abroad as I wouldn't want him to suffer whilst over there and he would feel guilty if he spoilt our holiday (which we would never make him feel like this). [redacted] is a polite young man who tries his best at everything. He pushes himself to his limits and most of the time ends up suffering as he wants to be "normal" with his friends. [redacted] also suffers from headaches at school due to the whiteboards and computer screens and lighting. I have bought [redacted] glasses from the opticians which have a slight tint on them to try and stop this occurring. In sport's at school he has to do games outside and he has to wear his p.e kit which is a short sleeve t-shirt and he wears a long sleeved under armour underneath it and jog pants with his hat and gloves and face cover as well. Some days he can only take part for 15 minutes and other days his teachers won't let him take part as it's too hot. If [redacted] could have the drug to give him a "normal" life now I would let him as I feel he's had a rough life up to now and if it stopped the bullies calling him names and abusive behaviour towards him he would have my 100% backing. I have had to fight for every little bit of help for [redacted], even had a two year fight with the GP to get him referred to the hospital at 4 years old. I had to be filmed for a t.v show to get help from the council to get my windows tinted so [redacted] could be safe in his own home. As working parents and a working family we pay our taxes and support people who need medication through more common conditions and through drug rehabilitation. I feel like throughout [redacted] whole life there has been a fight for everything we need for him. I for one will put up a new fight for the implant to be approved and I know that there would be many more people

	who would join me. Not only other EPP sufferers and their families but my whole community would be behind me for [redacted] Please do not hesitate in contacting me if you need any more information about [redacted] or photographs of how he covers up or his split lips or about his life in general [redacted] [redacted]'s mum

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Teacher
Other role	
Organisation	
Location	Wales
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Patients with EPP suffer extreme pain when exposed to the sun. I have seen first-hand what a debilitating illness it is as my brother-in-law is a sufferer. He has missed a number of family events due to not being able to be outside during the summer or if he attempts to join us he often suffers the painful after effects for days afterwards. By denying EPP sufferers access to the drugs which decrease their painful symptoms I feel that you would be discriminating against them, as this illness prevents them from taking a full part in family life, which impacts also on their families, and also prevents them from applying for certain jobs that require them to spend any time outside. Through providing these drugs people's quality of life would be immensely improved as well as taking away their pain and suffering.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	NICE are asked to consider the massive impact on everyday life of people suffering with EPP. Extreme pain from exposure to sunlight, results in total curtailment of participation in outdoor activities. The psychological effect on children not being able to play with friends should also not be underestimated, and long term impact on self-confidence is also significant. This treatment is proven to make a massive difference to everyday life for EPP patients and NICE are urged to given sympathetic consideration to its prescription for all those affected by EPP.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Imagine burning yourself on the iron or pouring boiling water on your skin, now imagine that level of pain on every part of your body that is exposed to the sun. A damaging, debilitating condition, damaging both physically and psychologically. Imagine being terrified to leave the house when the sun shines, imagine being unable to play in the garden with your children or take them to the park, imagine having to wear hat, coat and gloves on the hottest day of the year and being subjected to stares, to snide remarks and to bullying because of this. Imagine not being able to do your job because the office lights cause you pain. That is my day, every day, during any time the sun is out. Now imagine someone tells you that you can have a new drug which will take away much of this pain and suffering. That's what happened to me. This treatment is life changing. I've got a 3 year old daughter. Imagine being me when I have to tell her that "daddy can't come and play outside today". It's brought me to tears. It's single handily the only thing that's brought me to my knees and just cry for 30 minutes at a time etc. If EPP stops me working then the cost will be far greater than the cost of this drug. This is a pain that no pain killer can touch, a pain that no sun cream can prevent, a pain that leaves me permanently exhausted, but I carry on, because I have to carry on, for the sake of my sanity, for the sake of my marriage, and most of all for the sake of my daughter. Can you try to picture getting on a bus during summer, wearing a coat, a hat and gloves. That's what I have to do. I have to ask people to turn lights off for me, to close curtains and blinds. Some days I will be in extreme pain but show no outward signs, no rash, no swelling, no tan. There is nothing wrong with me? I'm making it up? I wish I was. This drug is life changing, not just for me, not just for my family, not just for my employer but for everyone affected by EPP.

	If I had cancer you would give me Chemo. If I was addicted to heroin you would give me methadone. If I had a bad back you would give me pain killers. I have EPP. What do you give me? You have the power to stop this pain, to stop this hurt and to stop this mental torture. The power to give me a life. You have the power to vastly improve my life, my family's life and other people with EPP in the UK. Please use this power wisely.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Local Government Professional
Other role	Social Worker
Organisation	
Location	England
Conflict	None
Notes	I am a children's social worker and have no connection to scenesse or any other pharmaceutical company
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	To be honest I wish to tell my story. I was born with EPP and have known no different. Since as far back as I can remember EPP has had an effect on my life, it has destroyed my childhood, where other children are able to play outside I had the choice of being socially included and enduring agonising pain during the whole of the next 48 hours or being a social outcast! I chose the outcast route as it was less physically painful. As I grew up I noticed people backing away from me as I couldn't join in normal social activities. It is hateful and there have been times when I pleaded with the devil, selling my soul to take this misery away. EPP still has a massive impact on my life and will do until I die unless there is a reprise from the daily misery of this condition. I would not wish this condition on my worst enemy. It also has an impact on my ability to contribute to society in a meaningful way. I can't stay outside too long owing to the reaction I experience, which is a tingle, the precursor to the burn that is inevitable which keeps increasing for at least 6-8 hours where my skin is on fire, I self-medicate to try and bring relief but to no avail. The worst part is knowing that while I feel this pain I can't avoid light the very next day which brings on more burning to add to the burn I already feel. The cycle goes on! All I want is after 47 years of life I can have some quality of life before my life is over. As I type this with one extended finger I am thinking about the pain of the light from my tablet screen and how my finger will burn later. I ask you to consider the use any drug to give others and myself a chance at life without guaranteed pain.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Manager
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have had EPP from as long as I can remember. I and now 51 years of age, but I remember having extreme pain after exposure to light, even as a small child. The pain is really indescribable to anyone who doesn't suffer with EPP. No one really understands how this condition affects you, unless you are of course a sufferer yourself. It is like your skin burning all the time, as if you've burnt yourself with hot oil or a sticky substance, where it penetrates under the skin. Nothing helps, no painkillers, no creams, nothing at all. You have to hide yourself away in a cool dark room until the pain subsides, which can take days. You cannot sleep at all as the pain is so severe, burning, burning all the time. You cannot bear anything to touch the skin as this sets another pain to add to the burning and can be a like a hot knife twisting into the skin. To try to cool the skin you have to put on cold water, but this only gives relief for about 30 seconds, but those 30 seconds are bliss. After that you return to the burning pain. The lack of sleep and the pain changes you as a person. You don't want to be bothered with people. This affects the whole family/s,they want to help and can't. You're short and grumpy with them as you are dealing with this severe pain and then to top that, the lack of sleep. You start to feel quite depressed and very low. You think about how you get escape the pain. You cannot share this experience as it is too difficult for anyone who doesn't have EPP to understand. Despair usually sets in at your lowest point and you get thoughts of how best to get out of the pain. This pain sucks all the energy and life out of you, so much so, there has been times I have for a short time, wanted to end it. We were born with this condition, to which there is no cure, but we have a light, excuse the pun, at the end of the tunnel and that is Afamelanotide. This would drastically change our lives. We could join in with family activities, walk the kids to school, play with them in the park, go to the shops, and any of the normal day to day things that most people take for granted. Instead of hiding away, avoiding the sun, staying in the shade and shadow hopping. This hermit lifestyle has its own toll on your mental health, as when everyone is enjoying the sunshine, you're on the side-lines watching and not being able to join in. Then there's being fully clothed in temperatures that everyone around you are in shorts and vest tops. You're having to wear

	longs sleeves, trousers, trainers, gloves and a hat, so you're baking hot and cannot get any relief from the heat and that's besides the ignorant stares and comments from people. This just gives you an idea of what it's like living with EPP and what life would be like with the help of Afamelanotide.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am married to an EPP sufferer and we have a son who also has EPP. I can confirm the massive, and detrimental, impact that EPP has on the life of the sufferer and all other members of their family. I note that your papers refer to the patient expert who states what a huge effect this treatment has on the Quality of Life, but that this is not effectively measured by the clinical experts. I would suggest that this difference is due to nature of the clinical measurements being defective. Historically all disease has been measured by how quickly it kills the patient. EPP is a chronic disease rather than a critical one, therefore the measurements need to change. My wife can be debilitated by EPP with swollen hands, feet, face, etc to the point where she cannot move her hands, or walk and is unrecognisable, with unbearable pain that no analgesic can control. There have been times when she has considered suicide just to make it stop. At the moment our Son, who is 30, seems to respond slightly differently in that he constantly feels exhausted, the more exposure to the sun, the more exhausted he feels. As he is married and hopes to have a family soon, this could have a major impact in how he is able to support his family in the long term. When younger he also suffered swollen face and limbs, but since becoming a young adult the exhaustion has become the prime symptom. In terms of cost, if there are 394 people diagnosed with EPP and the annual cost is £48,000 per patient then the total cost is less than £20M per year. At the moment the NHS spends £14Billion per year treating Type 2 Diabetes which is, almost totally, self-inflicted by poor diet and lifestyle. These 4 million people are able to continue with their appalling habits because the NHS keeps them alive with what has become extremely expensive medical intervention. If the NHS refused to treat Lifestyle Type 2 Diabetes then these people would have to choose between changing their diet and lifestyle or dying. EPP sufferers have no choice, they are born with this condition,

	and will die with it. Your clinical expert has stated that there is currently no effective treatment for this disease. This is a very effective treatment. This is dramatically innovative, and the most positive thing that I have seen in my 26 years working with EPP patients. It would be a complete travesty of natural justice for myself, my wife and our son, to continue struggling to work and, therefore, pay tax which is used by the NHS to treat people with Type 2 diabetes while we cannot get the only treatment for EPP that will actually work. By treating EPP it will enable all 3 of us to become more reliably productive and actually pay more tax into the system which will recover at least part of the cost of treatment. By treating Type 2 Diabetes all you achieve is to encourage those people to continue with their lousy lifestyle, have ever more health problems and cost the NHS ever more money. Quite simply, there is no justice in refusing to fund Afamelanotide.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Partner of EPP Patient
Other role	Social Worker
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My partner has an EPP diagnosis and currently is under [redacted] in London. He was diagnosed officially at the age of 35 and prior to this knew from an early age that he was allergic to the sun. This has severely impacted on his life and also us as a family. We have never been able to have normal holidays in the sun or days at the beach due to the reactions he may have after just 10 minutes. If my children have been to the beach or park with their dad it has been in the evenings when all other children are indoors or in bed. As soon as the spring is approaching this causes us all a level of anxiety due to the up and coming hot weather. If we are invited to a barbeque we cannot go until the late afternoon or any sooner then we have to stay inside when others are outdoors enjoying themselves. A day out or travelling to work consists of my partner wearing expensive tops, gloves and neckwear brought from the USA. He resembles a bank robber or a person who is up to no good and feels embarrassed that he looks so different, we are also concerned that he may be stopped by the police due to the levels he has to go to just for protection. When at work and in the building my partner is not safe from UV rays as he also can have reactions from the lights in the office. His job role requires his to visit service users and again travelling causes him reactions. If my partner should push himself trying to be normal for a very short time he becomes ill, irritable and has to go to bed which has impacted on us as a family when at home or on holiday. We have been excited at the thought of us being able to do normal day to day things with the new medication that has been approved. I do realise this is expensive; however this could dramatically improve life for my partner and allow him to not feel different.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	EPP Support Groups
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My name is [redacted] I am 53 years old and have EPP. I am one of five children who have different fathers, out of the five I am the only one who has had to suffer the torment of living with epp all of my life. I want to give you some insight into my life and why I am upset that the drug Scennesee is still not being given to patients as a matter of right to improve mine and others quality of life. This condition which is very rare has impacted on my life since I was a baby, during the sixties I was always crying during the summer and no one knew why, they thought it was many things but they never suspected that it was the sunlight that led to my extreme pain which is not understood by those who do not have the condition. In later years I have made connections to others who have this same incredibly debilitating painful lonely condition and now have some sense of belonging to a group of likeminded people who understand why I look strange dressed in thick clothing to stop the sun getting onto my skin during the summer months. Going back to my childhood the GP advised that it was the London air which unsettled me, they advised I should move near to the seaside as this “works wonders for many ailments”, not in my case It did not. In fact it made it worse, my mum naively took me to the beach most days to play in the sand and enjoy the seawater as well as feeling the cooling breeze on my skin. For a person with epp, this was the worst thing ever, as a baby I could not explain what was wrong, and there are usually no outwards sign immediately to indicate there is a problem, however dependent on how long I was in the sun it led to scabs forming on my nose, and further mickey taking as I grew older. My mum only knew that I was always crying and she and the medical professionals could not do anything to stop this. Eventually as I got older it was explained that I was allergic to sunlight. From his point on then at least I could avoid the light, however this led to isolation from family and friends. I grew up on a council estate, our playground was the streets the parks and the seafront. I did go out to play but so many times I became ill and was then having to stay in for days on end. I missed school, my friends nicknamed me “vampire” during the summer months. As a child this is extremely hard to cope with, I remember one day lying in my darkened room and looked at my

	hands which were on fire from the inside out. The hands were swollen as was my face and knees, but all I could see was my hands and I asked god, “why is this only me who has to suffer this pain all the time, my mates don’t have to put up with this”. My thoughts at that time were if I cut my hand off, will the pain stop? I was aged around 12-13 years and really wanted to do this. I told my mum who then made sure she kept a close eye on me to avoid such drastic measures. I was immature and naïve and yes it is a silly idea, but you know what even today at 53 at times I want to remove the pain, and feel like cutting them off again but I cannot. Another memory from a childhood with epp involves a games teacher at my all boys’ school it was the summer of 1976 and a heatwave was upon us. My mum wrote a letter to the games [redacted] who once given my letter asking to be excused from the games on the field called upon my peers, which consisted of two year groups. He asked me to stand next to him while he read out my mum’s letter. His words have always stayed with me; boys gather round, [redacted] has come up with the most feeble of excuses, he has written that he is allergic to sunlight (huge roars of laughter from my school year) [redacted] believes that sun hurts him, but in fact without sunlight we would not be here (more laughter). Even writing these words takes me back to that awful moment of being ridiculed in front of so many, and it makes me very sad to know that this condition of epp us still not known enough about and there are many more who are still suffering If the drug is made available then further ridicule of others can be prevented. Into my adult years the hurt does not go away, I do not get burnt as badly as when I was a child but the pain is still the same when I am caught out in the sun, or if tricked because I think the cloud is thick and I may be protected, I have got caught so many times and been in pain for a few days having to miss time with my family and also missing my paid work which is an indoor office role as I cannot risk being outside for long periods of time. I will bullet point what epp stops me doing to stop this becoming a rambling email, however what I do recognise is that once I start putting words down It brings back to me how much I have had to miss out on during my 53 years of life, • Days at the beach / park with my children • Missing school sports day • My children becoming embarrassed when I am fully covered, as adults they understand the condition now, but as kids I was the “weird dad”. • Not taking them to theme parks in summer, always

	going in the winter months. • The levels of anxiety when I planned days out and the sun was shining, I would be the only happy when it was thick cloud • Days out with friends to outdoor festivals • Having to endure being looked at constantly because I am wearing gloves jumper, long thick jeans to stop the light touching my skin. • Having to avoid areas where there are lights with UVA that hurts me. • I cover up while driving and have been questioned by police as to why I am wearing gloves and neck and face protector whilst driving. I now have to carry information leaflets to explain my condition from the BPA. • Summer holidays abroad, hardly ever • Holidays in the UK, yes but still got burnt so many times. • I studied for a university degree in my 40's, my face often got burnt due to the rays emitting from the computer that I was constantly sat at writing assignments • I had to turn down a friends recent wedding invitation as they are marrying on a beach. • Summer 2016 at my brother's wedding I had to be away from the main party under a tree as the wedding was held on lawns of a country house. • I now watch the summer holidays adverts on TV and it reminds me of the pain I have to prepare for again from March onwards. • While reading this to my partner today, I had not realised how much this has affected me, I started to cry when I recalled my childhood, it is probably as I have not been so open about this before. This took me by surprise, however it is a lot of trauma I have had to deal with for many years without support. • I was diagnosed in 1999, I found a magazine article that spoke of a child who could not bear sunlight, I took this information to my GP and an appointment was made to see [redacted] St Thomas' Hospital London. Being able to name the condition has been life changing, and I will now talk more freely to my colleagues and friends of my very rare condition.

	My whole life including the forming of relationships has been affected due to me not being able to out as any normal person, I have to plan ahead constantly to avoid becoming burnt and in pain. I have always prayed for a miracle to happen, I was told as a child that allergies have seven year cycles, I kept on hoping that my 7 year miracle would happen, scenesee has been discussed and tested for a number of years, please consider the impact this has on my life and that of my fellow sufferers. We just get on with it, but my life has been impacted greatly by this and I need to enjoy my later years of life being able to enjoy sunshine as much as the next person. Please reconsider the application and bear in mind that it is not only the patients who suffer, there is a ripple effect which affects my family, friends, work and my overall well-being in the world. Kind Regards [redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	
Notes	Only the fact if there is something that can help these patient as there is please release it
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My brother has suffered EPP all his life he is now 53 yrs old. As his sister and many other siblings and family members already know the pain and suffering their family member is going through.... It's horrendous the pain I saw my brother was in. One memory of many is my brother is 5 yrs older than me he is a good brother but I remember him being in his room I went straight in and saw my grown up brother crying in pain his eyes were so swollen they were closed his hands and legs had cold flannel on as they were the only help he had.... he shouted at me to get out I was so upset to see him like that. Another memory is my brother went away for a weekend trying to do something normal be a teenager and we had an emergency call to collect him, he was sitting in a corner in absolute agony. Please tell me why can my brother and other suffers of epp have the drug that can help them and stop their suffering. Why are you letting young children and adults continue to suffer it almost sounds barbaric please allow this drug to be used. From only 1 sibling of many who want to help their family.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Healthcare Other
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	How would I describe my pain? As rolling around naked in a field of stinging nettles.. can you imagine? All my life I have been bullied, isolated, misunderstood, shunned, picked on, alone, laughed at, alienated, mistreated and in constant unbearable pain. When I learned about Afamelanotide and what difference it could make to my life, I cried. Not because I thought I would be able to lay on a beach but because I would be able to do the little things "normal" people take for granted. Taking my children to school, watch them participate in a sports event, hanging out the wash, take my dog out, teach my son how to ride his bike and most of all, not feel different to other people and not feeling like people are sniggering at me and talking behind my back. To be able to sleep a decent night. Not being up in terrible pain. Not knowing how to get any relief. And now I learn you may take this away from me.. I feel sad, depressed and angry. If you had to live with my pain for just 10 minutes, this would not be up for discussion, this would be granted straight away. PLEASE consider our pleas. PLEASE change my life???

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Carer
Other role	Parent of EPP sufferer
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Hello, I am the parent of a 16 year old son who has suffered the effects of EPP since he was 4. No family history we are aware of. Please consider the severe pain sufferers endure with minimal exposure to not just sun light but even some indoor lighting. The suffering during a bout is heart breaking. The mental pressure this brings is also a huge concern, he's had to be excluded from activities "normal" kids take for granted. As he grows he will be excluded from most social events, festivals, holidays with friends etc - possibly leading to a "reclusive" loner life. There is currently little to alleviate the pain and certainly nothing to help prevent the onset and therefore allow a little more exposure to light. I'm sure you will be aware EPP brings possible complications with liver function and we really believe all lives should be enjoyed while young. EPP is a disability, would visible signs make the decision different? No cure and this drug is proven to be a huge help for sufferers in other countries. I ask you to reconsider this decision, or at least keep the discussion open until the supplier price is reduced. Regards [redacted] Parent.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In simple terms this drug would change my life. It would allow me to lead a normal life and to have a good quality of life. At the moment I live in fear. I am confined to my home and unable to carry out simple tasks that others take for granted but worst of all I cannot give my children everything they deserve. Unfortunately my 5 year old daughter also had epp and we are waiting to get my 1 year old son tested. I do not want them to have to feel the incredible amount of pain that I do and to feel trapped in their own home. I understand that the NHS is under immense stress but this drug really would change mine and my family's lives. I have had this condition since birth and it will never improve or go away. Please approve this drug so that is available on the NHS and allow me to lead a life that many people take for granted. I do not want to live my life in pain and in the shadows any more.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am an EPP sufferer and was diagnosed with EPP at the age of 32 after a lifetime of crippling pain and mystery surrounding what was wrong with me. I suffer year-long and am largely unable to spend any time outside. My condition has affected my life in so many ways, including mental health, career choices, ability to travel and experience so many aspects of life, as my ability to be outside is so limited. However 'being outside' is a misleading way of referring to it.. I have been told to 'stay indoors' 'not sunbathe' etc by many doctors; what people miss is the fact that exposure to light is not a choice. Many days a year I am unable even to walk from house to car, car to workplace etc. It is not a case of avoiding the sun by staying off the beach, shade hopping etc, there are days when EPP renders the sufferer unable to function without an incredibly high level of support, and perform even the most basic of everyday tasks without as a result, being subject to the most crippling pain imaginable. I have a ten yr old who, unfortunately, has been affected significantly by my condition. I spent 7 years as a single mother with a limited support network locally. She has experienced many days indoors when she should be in the open air, not watching her mum hide inside and cower at the faintest hint of light. I had hope when I was diagnosed, hope that after a life in the darkness, finally something could be done to improve my (and my family's) quality of life. I had hope developments were being made and some day in the future, my life could become closer to normal. The idea that we have an effective treatment that is potentially being denied to people like me breaks my heart. Here lies an opportunity for people like us to function on a day to day level, work in the jobs we want to do - and need to be successful in, be the kind of parents our children need us to be, and basically have access to the sort of existence others take for granted every day. WE deserve this. Please take all these comments into account, don't just read them, LISTEN to them. Realise the importance and magnitude of what could seem like a throwaway decision regarding an extremely rare condition. There may not be many of us, but we deserve better - we deserve access to a life of freedom and opportunity.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	With regard to the decision by NICE not to include Scenesse for reimbursement by NHS England, I would like to add the following comments in the hope that NICE will review their decision. Our 16 year old son suffers from the rare genetic disease called Erythropoietic Protoporphyria (EPP), the past few years have been unbearably hard for all of us. When he has a reaction, the reaction is like a horrendous burning sensation under the skin - like have boiling water burning you on the inside. Once he has a reaction, it takes a few days staying inside before the symptoms start to subside. Once a reaction has occurred even a hot room can exasperate the symptoms. It has a cumulative effect, in so far as, once you've had a reaction, over the next few days, any sunlight will cause an even quicker, often immediate, reaction to occur. The burning is so bad that it is impossible to find any relief and impossible to sleep. The only way to avoid a reaction is to avoid going outside in the sun. This has a huge impact on our son's quality of life. Can you imagine your child not been able to go out in the sun? He can't go outside at lunchtime at school. In summer he has often been sent home from school and missed lessons because the classrooms have got too sunny and hot (glass offers no protection either). He can't go out with his friends after school or see them on a weekend or in the school holidays - unless they are inside. Family holidays are a logistical nightmare and camping is impossible. Hats and gloves offer only a short reprieve, allowing him to go out for an hour or so, as the sun reflects off the ground and hits the face. Water is particularly bad for reflecting sunlight. Furthermore, once he's had a reaction, hats and gloves are no help at all - the heat of the day means that the reaction is maintained and immediate. Getting into a building asap is essential or the reaction escalates. Stepping outside again is impossible until the reaction has had a few days to calm down. The first reaction usually occurs around April/beginning of May and he will then be susceptible to reactions until October - that's 6 months of the year. He desperately needs this drug to dramatically improve his quality of life and his well-being, especially as he reaches

	adulthood and independence, with university on the horizon. As it stands, he is effectively imprisoned in bricks and mortar every summer - for the whole of his life. Please, please, please, put yourself in his position and imagine what it would be like not to be able to step outside into the sun, to be confined to indoor spaces all summer, to not be able to sit in the front of the car (glass offers no protection from the sun for EPP suffers), to not be able to go for a walk or a bike ride, to not be able to sit outside at a cafe or pub, to not be able to go into town with your friends, to not be able to go and visit all the wonderful cities in Europe, to not be able to go on holiday with your friends, feel the warmth of the sun on your face .... please, please, please don't let my son be a prisoner forever. This is a very rare disease and there are only around 500 sufferers in the UK, even less in England, it seems such a small price to pay for such a massively enhancing and life-changing drug. It's not going to have a small improvement in quality of life, but an absolutely HUGE improvement in quality of life for people with EPP. Thank you very much for reading my comments. Best wishes, [redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Public
Other role	Homemaker
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a mother of a 53yr old who has suffered EPP since a baby. I have seen him go through so much pain and swelling. As a child he was told he was allergic to the sun but could come in a 7yr cycle which of it wasn't. One day I sent a letter to have him excused from games and not only was he ridiculed by his peers also his teacher thought it was a hilarious excuse to get off games. This has stayed with him the whole of his life. He is now 53yrs old and over the years he has prayed this treatment to be available in the UK. Pease give reconsideration to allow the treatment to be used here. Like any mother I'd like to see no more people have to suffer like I've seen my son suffer. This treatment is as important as any other illness. Why are these people not helped?

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Europe
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Hi, I'm [redacted] from Hamburg / Germany, 61 years old. Since last Summer I got a treatment with Scenesse at the University CHARITE in Berlin. The only thing I can say: "WOW" My Life changed 100 % !!! Decades of heavy pain in the Summer are now over. Now I can play with my grandchild's in the garden and at the seaside without any Problems !! In five Weeks I will get my first treatment with SCENESSE for this year. EPP is not just a smart sunburn, it produce heavy pain just a few minutes after the skin is exposed with sunlight. Greetings to Great Britain and good lick to you. [redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Nurse
Organisation	
Location	Europe
Conflict	None
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear Sir or Madame, It is so important to approve of Scenesse. It changes the lives of EPP patients. Why deny a treatment with no side effects but with an immense benefit? Yours sincerely, [redacted] from Cologne, Germany My review of life being a 24 year old German EPP patient Being in the light filled me with insecurity, fear, anger and most of all with immense pain for almost all of my life. From having the first symptoms being two years old till three years ago when I first was treated with Scenesse living life was more than just complicated or difficult. The most simple things or daily life activities always resulted in me being in exceptionally strong pain. No matter how long I stayed in the light, no matter how much of my skin I covered up. It always ended in me being in pain. A burning, itching, sizzling pain. Deep in my skin. Feeling immensely hot, although my skin was ice cold. Scratching myself bloody to relive the pain for just a short moment. Very sensitive to pressure, to more light, to cold things to warm things.. Sensitive to everything. I could not bear my family comforting me because that meant even more pain. And all of this this would go on for days - sometimes up to seven days long. And going outside would only extend the time being in pain. But you have to go out. You have to go to school. Or to work. Or to the doctor. Or go grocery shopping. That is very hard. Especially when others do not see the pain. People do not believe what they do not see. They belittle your invisible pain. You have to explain yourself over and over again. You are always being watched differently and I always heard stupid comments on why I am wearing long sleeved clothes and a hat and an umbrella and gloves and shades. As a child being invited to class mates' birthdays I would always say that I do not have time on the day of celebration because I would know that it would end in pain. So I missed out on a lot of activities and normal childhood experiences.

	Looking back on my childhood and being a teenager I remember that every activity involving me included special measures to keep me safe but in the end I would have to endure pain. Me having sleepless nights. Drifting in and out of sleep and nothing would lessen my pain. I had hard times paying attention in school or even attending school. I was 16 when I started to take painkillers - morphine. And I was not like I was not in pain anymore - I was too high for the pain to bother me. My body and mind were not connected anymore and so I did not care for the pain. And I got used to the dose. So I would take more and more than the prescribed tablet every six hours. And it did not mean that the pain would be over faster. But that I would drugged till pain was bearable. I was lucky to not be in an accident during those times. My mom always referred to me as her basement-child. That is where I would love to stay. In the dark and cold - far away from the light. I never dared to dream of it being different. Of me not being scared going outside. Of me not always being in pain. But it changed! It has been three years now, since I first have been to Zurich to be treated with Scenesse. It is such a simple procedure with such a huge impact on my life. I am able to go outside for hours - into the direct light without covering up and without being in pain. Sometimes I still experience pain after being outside. But those times are very rare and the most important thing is that the pain is not nearly as intense and not as long as before. It is just like a normal mild sunburn. My self-confidence has grown. I am not afraid to go outside anymore. I do not have to plan every single step. I generally think more positive. I am more open minded. I have more possibilities. I am able to take part in life like anybody else without a disease. I have not taken a single painkiller for the EPP symptoms in three years. I do not feel like an EPP patient anymore.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Wales
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My husband suffers from EPP. At times, it has left him in severe pain. His skin swells and is red, you can feel the heat coming off his body from a distance. It affects his mood. He can't sleep. Even the slightest light/water/touch of anything to his skin causes him severe pain. We have to sit in the room with lights/tv off as these will add to his already agonising pain. We can't go on family holidays unless its grey out or it will cause him distress. Our two sons are missing quality time with their dad because when the weather is nice outside and we want to play out, he has to hide inside. He goes whole days in summer not leaving the house until evening when it's starting to get comfortable enough for him to go outside. Usually after bedtime for our children. When we've been for days out to farms etc he has to hide in shadows while wearing hat and coat and gloves. He has to avoid outside as much as possible. This has severely affected our relationship as well as with the children. They have got used to "daddy can't go out in the sun" "daddy burns in the sun" and will automatically assume he's not going anywhere with us. When we are in the car any time of the year he needs to wear gloves and coat to keep covered. He still hides his hands out of direct sun regardless of gloves in summer as it still burns thru. When he was taking part in the drug trial he was able to spend not just minutes outside but hours, in a t-shirt, with us as a family and didn't suffer. He was happier, healthier and was able to feel "normal" for that time. Now he is depressed, always in a low mood, lacks interest in doing anything and it is physically affecting him too. He is on medication for lack of vitamin d. He has been suffering with constant illnesses from a low immune system. Every year he starts to suffer earlier than the last and the reaction is worse. It is a debilitating illness. This drug is life changing. Not just for those who have EPP. Those of us who live with people with it are also suffering. Please let us have a normal family life. If you saw the look on a child's face when you tell them for the hundredth time that "no daddy isn't coming" your heart would break too. Like mine does when my sons want to play with their dad and he can't because he is either suffering now or will later. I see him force himself to get out to try and spend time with

	them and I see him suffer afterwards. I can't watch someone put themselves through that agony. Can you? Please give us our lives back.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Carer
Organisation	
Location	England
Conflict	
Notes	I am both a patient and a carer as my son and I both have Erythropoietic Protoporphyria
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have read all the documents pertaining to the application for Afamelanotide to be made available to treat Erythropoietic Protoporphyria (EPP) and attended the first Scope Workshop held by NICE in 2016 as a British Porphyria Association member and EPP sufferer. So, I am aware that I cannot offer new evidence with respect to the need for this treatment. I am asking, however, that the following be given consideration. I have EPP with severe intolerance to visible light which became active when I was 1 year old (diagnosis was at age 22). My life has been completely dictated by EPP with respect to education, career and life style. As a young child I experienced such extreme pain that, before the age of 12, I had decided that suicide was a viable option if the pain made life unbearable. I thought this was a smart decision. It was only as I got older I realised that this was not something that would be considered a normal way to live. As an adult I have had more control and autonomy and have made life choices around the constraints EPP imposes. I am dependent on prescription drugs and addicted to the pain relief drug codeine. I have two children. My decision to have a family was based on the genetic/hereditary evidence available at the time which I started my family which stated that the chance of passing on EPP, with symptoms, was highly unlikely. Unfortunately, this data was incorrect and research that took place after my children were born revealed that the chances of passing on the condition were much higher. I would not have had children if I had had this information. My daughter (now 20) has the EPP gene but does not currently have symptoms although these could still develop and she could pass EPP to her children, should she choose to have a family. My son has the EPP gene and developed symptoms when he was 8 years old. My son is now 17 and the last 9 years have been unbearable as he has an extremely low tolerance to a very wide range of visible light including a range of artificial light as well as natural light. My son failed at school as it was impossible to provide a safe environment for him. Eventually, we obtained an Education and Healthcare Plan to support him which has enabled him to

	attempt education at a sixth form college. This requires a support team which includes transport (a taxi) provided by the County, site personal changing areas of the college so my son can be safe while he studies, a one-to-one coach to enable him to catch up on work missed due to his health and access to a counsellor I have had to give up full time work and am his carer working part time around his needs. Last year I was on the verge of bankruptcy but my Father's death and a small inheritance has kept us afloat. My daughter, despite being symptom free, has had a life dictated by EPP and has had to act as a carer for both of us. My son has a proactive consultant who managed to make a red cell exchange treatment available for him. The aim to try and provide him with temporary relief from the terrible pain and stress of trying to avoid light. This procedure is, obviously, extremely expensive and needs a multidisciplinary team to facilitate it. The procedure works by removing red blood cells containing high levels of porphyrin and replacing them with donated red blood cells thus reducing reaction to visible light for a temporary period. Unfortunately, my son's veins cannot stand the procedure so it has only been successful 50% of the time. It has been extremely painful with his veins collapsing and permanent scarring from a femoral line. Additionally, he suffers from extreme fatigue and low blood pressure after the treatment with recovery time taking a week. Even so, throughout 2016 and the early part of 2017 he continued to attempt the treatment on a regular basis in the hopes that a successful exchange would give him respite from the terrible pain he is in and to allow him to have short periods of time when he could experience a more normal life. The difficulties and lack of success with the procedure means that he has had to give up and has not attempted an exchange for 6 months. As has already been well documented there is currently no medication available which can provide relief from the pain caused by EPP. Since June 2017, due to extreme constant pain and the anxiety of trying to avoid visible light, my son has resorted to using high strength cannabis in an attempt to make life bearable. This does not reduce the pain but it does make him able to get better sleep and have less anxiety. My son has lost 2 stone in weight and his personality has changed, he is dependent on cannabis and has tried other illegal drug options trying to find pain relief. It is possible that this course of action could kill him but, unfortunately, I cannot stop him as I have no alternative to offer him and have been suicidal myself with the condition. My son and I have met, either face to face at support meetings, or through internet access many people from around the world who suffer from EPP. Every single person has their own EPP my son and I are evidence that the condition differs from person to person but the common symptoms already well documented

	are consistent across all suffers. There is absolutely no documented evidence to suggest that those with EPP in England require Afamelanotide any less than EPP suffers from other countries. EPP is a unique condition, it is impossible to compare it with any others because they do not exist. All organisations use standardised matrix/guidelines to make decisions about “need”. Therefore it is extremely difficult to obtain any support in the form of Personal Independence Payments or Employment Support Allowance and so people in England with EPP have no treatment and no support. Finally: my son met a young man with EPP. He is American and became so ill with EPP both physically and mentally, that his parents flew him to Europe for an Afamelanotide implant. This was privately funded and something he now does on a regular basis. He is currently in good health, good spirits, he has graduated and is leading a happy life with a good job. I watched him talking to my son who is emaciated from using illegal drugs, scarred from the red cell exchange attempts, in permanent pain, suffering extreme anxiety trying to avoid light and can see no future for himself. This is not something I would wish any parent to have to witness.

Comments on the ACD Received from the Public through the NICE Website

Name	
Role	Patient(s)
Other role	Board members of "Selbsthilfe EPP Germany"
Organisation	German EPP Patient Association
Location	Europe
Conflict	None
Notes	The board members of the German EPP Patient Association [redacted]), please find our patient's testimonies below.
Comments on individual sections of the ACD:	
Patient 1	"Dear NICE Team, I have heard with horror, amazement and incomprehension of your decision to deny the British EPP patients the drug from Clinuvel. Our daughter is also suffering from EPP. We have been looking forward to every rainy day for the past 10-12 years. We and especially our daughter count the days until she turns 18 and finally gets the implant. There are only 356 days until her birthday :-) How can you make such a decision? I am describing to you some situations from the past years that I could not relieve my daughter, I could not help my daughter and save her from pain. But you could do this for all waiting EPP patients in the UK. This first episode does not seem very restrictive, but shows that we have tried to make the best of the situation: during the holidays and on bad sunny days we sat (me with our daughter and her little sister) until about 16.30 in the darkened room watched TV or played games. When the children were younger, they slept at lunchtime, and we went off in the garden or to the playground after dinner. All children had to go home, but our girls were allowed to play outside for a long time (without other children). In solidarity, our younger daughter did not drive with her friends to the outdoor pool! She stayed with her big sister. Our daughter quickly sensed whether it was a good or bad day, on bad days, the skin began to tingle after a few minutes. Then she was not able to cycle to school (15 minutes). I always drove her by car. Physical education in the open air often could not join you and had to look under your special UV umbrella in the shade. In the summer and on bad days, she always wore long-sleeved shirts and long pants. If she wore short clothes, she stayed in the house or had infernal pain in the evening. On school trips, she often stayed in the youth hostel or in other classes, as she could not take part in many actions outside. or she took the pain because she wanted to be with her friends. For me as a mother, the worst thing is to see her cry in pain, scream and suffer. I can’t take her in my arms and was not

	even allowed to comfort her, as my body heat is unbearable for her, as it makes her pain worse. When she fell asleep in the evening with complete exhaustion, she often flinched in pain in her sleep and woke up again, as there was heat in the bed, which intensified the pain again. You certainly have not comforted a child who cried “Mum even my tears hurt me” Even normal things are not possible: look forward to the first rays of the sun => no, they even scare us eat outside in the garden with the family => we go out after 20h, picnicking with friends and family => we do not participate or plan outdoor activities bike tours, sports outside (jogging, hiking, swimming, etc.), sightseeing, city tours, driving when the sun shines in the car, sitting in the classroom or on the bus at the window side, etc I hope and wish that my words will make you reconsider your decision and give the English EPP patients the opportunity for a carefree, ""normal"" and that’s the most important point: pain-free (!) life. Best 'cloudy' regards [redacted] Germany"
Patient 2	"Life of a six-year old girl with EPP: I am a mother of a six-year old girl in Cologne, Germany, describing hereafter our everyday life. This congenital disease just isn't comparable to any other due to the fact that most of the physicians simply don't recognize it. And the patient is left on his own with his awful pain. I am a nurse and I know one or two things about suffering. My daughter was one-and-a-half-year old when we first experienced the EPP effect to its full extent. And that happened after FIVE minutes in the sunshine! All of a sudden our daughter started to scream, tried to cover her face, while simultaneously scratching her hands. It was a crazy situation for we could not see any reason for such a behaviour. Various physicians were clueless and sent us back home. The girl was screaming all day, crying at the least, she was unable to eat anymore and just couldn't calm down. Even the nights couldn’t give her any ease, she kept whining, too tired to cry. This situation lasted five whole days, we were desperate and going mad. On the second day in bed and not exposed to any sunlight my daughter’s face was completely swollen. She could hardly open her eyes. Her nose and lips were just as swelled, as if she had been in a brawl. Arms and hands were swollen, too, her little body just looked bizarre.

	Again, we desperately looked for help but the physicians couldn't offer any solution. Nothing helped ease the pain - no painkillers, - no cortisone - no antihistamine. NOTHING worked. The kid kept crying all day long. On the fifth day she started blistering, her lips, nose and forehead, even her hands were covered with blisters. The physicians were completely perplexed. This was our first encounter with EPP, unfortunately just the start of an endless story. As a mother of a five-year-old kid I started investigating, hoping to relieve my daughter's suffering, somehow. And ended up with a physician, some 300 kilometers away, who diagnosed EPP. We now know that illness's name but the suffering is still urgent. Our child's life is extremely limited, she simply can't enjoy a normal childhood. She is unable - to go to any birthday party during the summertime, - to go to the beach - to play outdoors - to participate in any kindergarden activities At this young age, isolation has already begun at her young age. We, her parents, dare not imagine what her future will be like. [redacted], Cologne, Germany"
Patient 3	I am suffering from EPP and do not understand how patients can be denied a medication that will make their life bearable. Bright light or sunlight for only a very short time lead to unbearable pain. Every part of the skin becomes extremely sensitive against heat and cold. No sleep, only extreme swelling that disfigures you. For 65 years I have endured this, and it has shaped my whole life. I was alone and excluded. In 2017, I got 4 Scenesse implants, and NOW I FINALLY KNOW WHAT LIFE REALLY MEANS! I do not want to go back, ever. PLEASE, make Scenesse available to everyone, so nobody has to suffer needlessly anymore. [redacted], Herzogenaurach, Germany"
Patient 4	Last year, in 2017, I was implanted four times with Scenesse, and it has changed my life almost completely. I was able to

	tolerate much longer exposures to (sun) light, and that even on consecutive days! This does not mean I am free of any phototoxic reactions, but it's SUCH an improvement! Biking to work, going shopping or going for a longer hike outside, all that is possible now! So the overall result is positive: while Scenesse does not protect from every phototoxic reaction, is is very effective in lowering the pain intensity, and making the pain subside very fast. [redacted], Germany"
Patient 5	Dear NICE team, When I heard and read that the NICE plans to not make Scenesse available in the UK, I could not believe it, are you even aware of what you are doing? I am 42 years old, have been diagnosed only 5 years back, but have been suffering from EPP for all my life - and especially as a child, life with this disease is HELL! You cannot go outside to play, you cannot make friends, because you are socially isolated, and you are constantly AFRAID! And NOTHING helps against the pain! Imaging someone holding your hand in boiling water! THAT is what you are condemning every EPP patient to! You say that Scenesse is not effective. Let me tell you from a patient's perspective who has had the medication: it is more than just "effective"! I was implanted for the first time in my life this year, and where before I could bear only minutes of light on a summer's day, I can now go outside for SEVERAL HOURS EACH DAY! Not just a few minutes, but HOURS! If that is not an improvement, I do not know what is this medication has changed my life! For the first time I could sit in a café, I was able to take a walk outside with friends, without the constant fear of being exposed too much and being awake the following night because of the searing pain. Before, sometimes, you just ignore the warning signs, because you do not WANT to be alone anymore. And you dearly pay for it! I do understand that clinical research in rare diseases is difficult, but if you do not have enough data to make an informed decision, then PLEASE wait for the data being gathered now, and I can tell you, it will make clear how well this medication works! Please do not take away the patient's ONLY opportunity for a somewhat normal life! Imagine your child or your parents suffered from this and then ask yourself if it is ethical to deny them everything you yourself take for granted! Thanks a lot for listening, [redacted], Biberach, Germany

Patient 6	"My name is [redacted], I am 62 years old and although the symptoms began in my childhood, I was 50 years old when I was diagnosed with EPP. After the diagnosis I found the patient association and was lucky to be part of the first double-blind clinical trial of Scenesse in Dusseldorf. When I was getting the non-placebo implant, the summer was a wonderful and I enjoyed it with all my heart. Suddenly I was able to take a walk or ride a bike in the sunshine just like a normal person, without fear of EPP symptoms. During those weeks I did not have to stay alone at home to protect myself from the sun. Unfortunately it took several long years, before the medication was available again - last August I got my first implant, and would not want to miss it anymore. You do not feel isolated any longer, and there's no more sleepless nights due to the pain. I hope every patient will get access to Scenesse as soon as possible. Kind regards, [redacted], Germany"
Patient 7	Dear National Institute for Health and Care Excellence UK (NICE), Deciding not to recommend a life changing medication for people suffering from EPP would not be nice but nasty. I am suffering from EPP myself. A few years ago, I had the chance to try the new medication called Scenesse (Afamelanotide) myself during a clinical trial. Before this I really suffered from EPP. I could not spend my daily life outside like other people. Even normal activities like picking up my kid from school, spending some time at a playground, in our garden or simply doing the groceries always have been a challenge as soon as there was too much light involved. Extra activities, like bicycle tours, open swimming pools and holidays were impossible for me. Light was my enemy and pain was my unpleasant companion. When I started to take Scenesse medication it changed my life. I was able to do all these normal things with my kid. Walking on the sunny side of the road and the sunny side of life! It was incredible for me! I was even able to drive two hours per day in my car to attend a study course. This great time with a nearly normal life ended after the trial was finished. The EPP pain is back and I am suffering again. Now I have two kids, one of them severely disabled. And the new challenge is to cope with EPP having a kid that won't understand why mommy can't go outside. I am now waiting to get treated with Scenesse again. Want to

	get back to the sunny side of life on the sunny side of the road! Here in Germany I have a realistic chance that this will become reality. However, people in the UK won't have this chance if you refuse to recommend Scenesse as a treatment for EPP patients in the UK. [redacted], Krefeld, Germany"
Patient 8	To the NICE team: Mary Hughes, Raisa Sidhu, Sheela Upadhyaya Dear Ladies and Gentlemen at the board of NICE You are responsible for the treatment and a better life for people in UK, who are suffering because they have the very severe disease: EPP. My name is [redacted] of the German Patient Association Selbsthilfe EPP and mother of a daughter suffering from EPP. She is now 24 years old and has been getting the treatment for more than 3 years, first in Switzerland, now in Berlin. And I quote her, when I tell you: She has got a new life. Only with this medication she could survive all the demands in learning to be a nurse in the University Clinic in Cologne and can work every day! And after terrible times in her childhood, she has now a life without pain and social isolation. Because her two elder sisters do not have this disease, you can be sure, that I am a good judge of life in childhood when a person is suffering! No living in the light is possible, social isolation in summer has an end, because she couldn't play outside, couldn't take part sporting activities, has no chance to be part of holiday activities in the summer and all the year outside. Meeting friends is an important factor to become a strong person. We as family are happy, that she grew up with love and help in our family but it is no comparison with life with "Afamelanotide". Indeed, she has a new life!!! And as the [redacted] of the German Board, I got to know many comparable stories of German patients, children, adults, old people, male and female. Not rarely, depression, problems with drugs, alcohol, addiction, and suicide are combined with this disease. And I am so happy, that in German Health Policy all responsible people after considering the facts said "yes" to helping all suffering people, making this medication accessible to all patients. What is the problem in UK????? Even the UK did sign the International Human Rights many years ago. And it's a human

	right to live without suffering if it's possible. And I think in your Health Policy one point is: Quality of Life!!! Please reconsider your vote!!!! Herzliche aus Deutschland [redacted] Overath/Cologne [redacted] Selbsthilfe EPP
Patient 9	My Name is [redacted] from Vaihingen, Germany. I am a patient suffering from EPP for now 40 years, I am in the absolutely lucky situation to get Scenesse since last year. I couldn`t imagine that I can stay some time in sunlight without having indescribable pain due to the sunlight. Due to the wonderful medicine Scenesse I can feel first time in my live that the sunlight can create a warm and fine feeling on my skin. If someone told me that, I would never have believed it, but it is absolutely true. So please allow the British patients suffering from EPP to have that outstanding, wonderful and only medicine Scenesse for their life. They just want to live a normal life. Please consider this on your decision. Best regards, [redacted]
Patient 10	As a patient suffering from Erythropoietic Protoporphyria, I was part of the Phase III, double-blind, placebo-controlled study of Scenesse, at the University Dusseldorf. The medication was implanted into my skin, and after only a few days, I could feel the effects, that would last for 6-8 weeks. For the first time in my life, sunlight felt warm on my skin, and did not cause any pain. Since birth, I have been suffering from EPP, like my mother. Since there were no visible symptoms, we were often misdiagnosed as malingerers. Neither friends nor relatives would believe me, and proposed that I was only imitating my mother. For decades, my disease was misdiagnosed due to missing knowledge on the physician's side, who also banalized my symptoms. Only at the age of 36 (in 1999) a dermatologist finally diagnosed EPP. He sent me to the Dermatology of the University of Dusseldorf. At that time, there was a longitudinal trial going on, investigating EPP and its possible treatment. I took part in that study, and for two years, I was given different medications, including beta-carotin, Vitamin C, Vitamin E, Lysine, but none of that worked. EPP is a highly impairing disease when it comes to quality of life: during the summer months, there's no activity outside possible. Every step in the sunlight is overshadowed with fear and worry. Tinted car windows, sunshades, or similar things do not provide enough protection from the light. Even short term exposure to sun or light in general, also when its overcast, induces the symptoms: it begins with itching, rising skin tension and over time turns into extreme, burning pain and swelling of

	the skin. Even the strongest pain medication does not alleviate the pain. The symptoms subside only slowly, this takes days. And during that time, your perception of cold and heat is massively disturbed. Normal room temperature of 20°C as well as water at body temperature is perceived as burning hot, and will intensify the burning pain. Cold tap water fells like ice, and lower room temperatures lead to a freezing feeling and shivering. In the winter months the symptoms are less frequent. Depending on weather and light intensity, the risk for phototoxic reactions gets bigger with the beginning of spring and stays with me until late autumn. The first problems will turn up on parts of the skin that are exposed the most (face, head, ears, lower arms, elbows, hands, calves, knees, feet). The only way to stay safe is to keep to inside rooms. If you cannot prevent outside activities, or long drives with the car, I try to protect myself by wearing a baseball cap, long-sleeved tops and trousers, gloves, socks and closed shoes. You can imagine it's a torture during summer. Strange looks from other people I have learned to ignore. Scenesse would so much improve quality of life for me! [redacted], Dortmund"
Patient 11	To the Nice Team. I am a 51 year old suffering from EPP and will tell you of my tale of woe, so you can better understand what massive, painful, mental and physical effects EPP has on my entire life! Since I was young I would get extreme pain after sun exposure, like sunburn but much stronger, ad holding for days. Most of the time you do not see that there's ANYthing wrong with my skin but it feels like burning myself! Not one painkiller helps against the terrible pain. You can relieve a bit of the pain by using cold water, cool packs, cold poultices and the retreat to a dark, cool room inside. I endured countless visits to the physician, but got diagnosed as a malingerer since there were no visible symptoms. So I did no longer go to any doctor. I withdrew myself more and more, became isolated and was more often than not the odd one out. There were no outside activities with friends, like swimming, biking or any other kind of sports, and even my daily route to school was very painful. And picking a job was difficult as most of the professions I was interested in were a no-go: farmer, florist, veterinarian or architect. When I was 20 years old, I finally got the right diagnosis: I suffered from the rare metabolic disorder Erythropoietic Protoporphyria (EPP) and not a simple sun allergy. Finally the problem had a name and I had hopes to find a cure or at least some relief. The dermatologists in the university in Dusseldorf and I tried everything without success. So, another let down, more frustration, doing the best despite the problems, more

	isolation, more loneliness. Only wearing long-sleeved clothes made from tightly spun cotton, jeans, jacket, hat, gloves and using an umbrella helped me survive everyday life. During the worst times, I wore a cloth hiding my face. But even that would only protect me for a short time. And you are sure to attract stares from everyone. I have adapted my whole life to my disease. And as a mother of three children, all problems repeated. There no way to go to the playground with them... Joining my kids on their way to kindergarten or school was problematic, and being with them on school trips or events impossible most of the time. For me, there were no holidays at the sea, in the mountains or in the south, no going to the swimming pool, not until today. My kids were able to do all this with friends of ours. But I was alone, in the dark, wanting to share these memorable moments WITH them. Since June 2017, I am being treated with the only medication that helps if you have EPP: Scenesse. I have not had ANY side effects, and I am overjoyed and so relieved! My life has changed massively to a really good end: after I started getting Afamelanotide, - I was able to make a bike tour during summer for the first time in my life - I was able to travel to work without the protective gear I described above, or just be outside - I was able to work in the garden, go for a swim, bike, hike, and simply enjoy nature - I seldom feel pain, and if I get too much sunlight and do feel pain, it is gone the next day - I can be with my friends when they do something outside in summer - I do not have to separate myself from others - I am much less often alone, and I am more sociable and cheerful - I can do sports outside After 51 years, this treatment enables me to live an almost pain-free, normal life! Finally, a life worth living, a life fit for a human being! For me, the denial of treatment with an already approved medication constitutes a failure to render assistance as well as a form of criminal assault on all EPP patients in the UK. After all you just heard about the positive effects of Afamelanotide, can you really stand by your decision with a clear conscience? With that decision, you will be complicit in causing more pain and harm we EPP patients already have enough of! Every single EPP patient has a moral right to that treatment, since it is

	proven to be effective and has no side effects. No government agency should prevent patients from obtaining this treatment! [redacted], Lohmar, den 22.01.2018
Patient 12	"I am a 53-year-old patient, suffering from EPP, like my older sister. And when I say “suffer” I mean it. Up to this day, dealing with this disease was excruciatingly painful. No matter whether it was as a child or an adult, the disease demands limitations and adjustments to your life, always. I really could have done without these painful experiences, but I could not simply go into the next shop and buy a new body! So I always had to take my handicap into account when planning my life. Unfortunately EPP is not my only handicap, but the most severe, since it limits my life’s choices: It is horrible if you cannot make friends as a child! It is horrible if your disease limits your choice of profession!! It is horrible when your personal happiness is being governed by a disease!!! It is horrible to suffer from EPP if there is a medication for it!!!! It is horrible that even in this enlightened and wealthy time, the arbitrary decisions of some lead to the suffering of many. That people who do not have to suffer indeed have to suffer. This is torture and certainly violates any human rights! To completely list my tale here would be too much, let me say this: EPP is with me 24 hours a day, my whole life through, almost 53 years. If I had not adapted, I would no longer be alive to some degree, the adaptation works, but it comes at the cost of deprivation, excruciating pain and hardship! It is inhuman to deny suffering patient access to this medication! Why? Monetary reasons? This is incomprehensible! Please reconsider your decision about this medication. Otherwise you deliberately deny a suffering person the relief so desperately needed. Please vote for the approval of Afamelanotide in the UK, the only working medication for our condition, a drug that massively improves the quality of life for the patients and has no severe side effects!!!! With kind regards and in hopes for a positive vote from your side, [redacted]
Patient 13	"[redacted], Germany My son (20 years old) has been treated with Scenesse for the last two years, and his life has completely changed for the better! It took about two weeks after setting the first implant,

	that the first effects became visible, a slight tan and pigmented moles appeared. After careful acclimatisation to the sunlight (he avoided the sun as much as possible up to that time), he discovered that the sunlight could feel pleasant on his skin after the second implant, the effects got more pronounced, and he was able to go outside without having to worry, he could take his bike to university and take the car on his own. The burden he had been carrying just fell away, and his permanent abdominal pains, symptom of his constant psychological strain simply disappeared. Not needing to explain himself all the time, not needing to abstain from what he wanted made his daily life lighthearted. He simply began to LIVE!!!

Received by NICE on 10 January 2018

Dear Dr. Upadhyaya,

My name is [redacted] and I write to you on behalf of all patients with the ultra-rare light intolerance erythropoietic protoporphyria (EPP) and particularly of those in the UK, recently affected by a disappointing recommendation by NICE. As I am in the fortunate position to live in Switzerland, I have access to the afamelanotide (Scenesse®) treatment since 2012 and was chosen as a patient representative for EPP during the approval process of afamelanotide at the EMA.

At the last World Orphan Drug Congress in November in Barcelona, you vividly explained that the NICE appraisal process for Highly Specialised Technologies takes into account the specific limitations and challenges of every individual rare condition. Reading through the consultation documents published by NICE on December 20th, however, it became evident to me and the other members of the recently built Working Group of EPP Patients with Background in Science and Medicine, that the uniqueness of EPP has not been adequately taken into account during the appraisal of afamelanotide at NICE and that the real benefits of the therapy have not been recognised:

In EPP, exposure to even a few minutes of sunlight and strong artificial light sources causes massively painful phototoxic reactions and severe burns in the vessels of the exposed skin, from childhood on. With afamelanotide EPP patients can significantly increase their exposure to light and experience less phototoxic reactions and, when developing them, these are of less severe nature: The treatment enables them to significantly improve their physical and mental health, and they become more integrated into society. In the NICE appraisal documents, however, the Evidence Review Group expresses uncertainty about the true extent of the benefit of the afamelanotide treatment in EPP, commenting that patients and specialised clinicians report hours of pain free sun exposure under therapy, while in the trials only minutes of additional sunlight exposure could be measured as compared to the placebo control group.

I now would like to make you aware of the important aspect that the trials were conducted under quotidian conditions. This means that the measured sun exposure times were limited not only by the onset of pain, but also because of working hours and other factors like rainy weather, during which trial participants were not exposed to sunlight. The trial outcomes are expressed in mean daily values per patient, i.e. the sum of the exposure times to sunlight divided through all days without pain during the study period, including for example also the rainy days. Such a standardisation obviously cannot capture the full extent of the therapy's benefit. On the other hand, in their testimonies patients report of individual days during which they could be outside in sunlight for several hours. But this was only possible because on those days they did not have to work, did not have other duties indoors or the weather was not rainy.

For the patients, being able to manage the few minutes they have to be outside to go to work without having to worry about sunlight is already a significant benefit. However, the true extent of the effect is much bigger as illustrated in the patient testimonies: Hours of sunlight exposure become possible under treatment. The

described effect is comprehensible and also not unique to EPP: A friend of mine has severe migraine, and having found an effective medicine that she can use when an attack occurs is a major reduction in disease burden for her entire daily life, 24 hours a day, 7 days a week, although the attack itself usually only lasts for 48-72 hours. For a migraine medicine, a mean annual reduction in headache time would underestimate the true benefit of the treatment. Likewise, the efficacy of afamelanotide in preventing the occurrence and severity of phototoxic reactions in EPP is significantly underestimated when averaged out over the total duration of a clinical trial.

EPP is an ultra-rare condition associated with known limitations in measuring the efficacy and benefit of any therapeutic intervention, like the considerable disease heterogeneity, the extreme rarity, and the lifelong conditioned behaviour which leads us to avoid light and sunshine at any cost in order to prevent having to feel the debilitating pain of our disease. We should not be denied access to the only treatment for our condition because of limitations in demonstrating its effect by conventional study designs and we are determinedly committed to making our voices heard loud and clear about our right to lead a dignified existence thanks to afamelanotide. To this end, we founded an international working group of EPP patients with a professional background in science and medicine. Currently, we help patients in all countries understand the scientific documents in order to be well-prepared for their involvement in the national regulatory and HTA processes, and with our support patients in the Netherlands, Germany, Italy, Austria, Switzerland and the US have already been able to contribute to making the afamelanotide treatment available through their respective national health systems and/or their medical insurance programs

I hope that I could raise your awareness about the important fact that the standardised trial outcomes should not be confused with the real benefit of the afamelanotide treatment in EPP: We severely suffer from light deprivation and the intense and excruciatingly painful reactions caused by a few minutes of light exposure, and no other effective therapy is available for our condition, and the benefit of afamelanotide is experienced by patients, including myself, as life changing. I urge you to please support British EPP patients, end their inhumane suffering and light deprivation, and make the normal life we are able to have thanks to the afamelanotide treatment possible for them, too.

Please, do not hesitate to contact me, we would be happy to further elaborate our points with you and discuss possible ways to support the NICE appraisal process. I am looking forward to hearing from you soon.

Yours sincerely,

[redacted] and porphyria expert, Germany and Switzerland

[redacted], Austria

[redacted] and porphyria expert, Italy

International Working Group of EPP Patients with Background in Science and Medicine

SCENESSE® (AFAMELANOTIDE 16mg) BUDGET IMPACT ASSESSMENT ENGLAND

CLINUVEL MANAGEMENT

Melbourne, [redacted]

INDEX

PREAMBLE

The budget impact assessment prepared by NICE and sent to CLINUVEL UK on 12 September 2017 requires discussion and further analyses in order to ensure that an accurate projection of the distribution of SCENESSE® (afamelanotide 16 mg) for the treatment of erythropoietic protoporphyria (EPP) in England is taken into account by NICE and NHS England.

The analyses in this document provide a justification for the projected future budget impact of SCENESSE® in England, and CLINUVEL assumes responsibility for the provision of this data to NICE and NHS England.

The premise of the approach taken by CLINUVEL is that it wishes to be precise in its assessment of the development and commercial distribution of SCENESSE® in Europe and Switzerland and to ensure that there are no unanticipated and surprise economic burdens for healthcare budgets in any country. CLINUVEL has focussed all its resources and staff the past 12 years on researching, developing, and distributing a novel medicinal therapy for EPP and the Company has been compelled to know all aspects of the disorder, the patient population and the health economic consequences per country. CLINUVEL wishes to set an example in the sector by delivering each individual nation an unequivocal submission of patient data which can stand up to future rigorous review.

EPP is a genetic metabolic disorder due to a defect in ferrochelatase (FECH) located on the long arm of chromosome 18 (18q21.3). Due to this enzymatic defect, tissue accumulation (skin and liver) of protoporphyrin IX gradually occurs, causing anaphylactoid reactions and burns (phototoxicity) in EPP patients. EPP patients are seen by a vast number of medical specialties due to the fact that there has never been one specialty prescribing an effective therapy, prior to the use of SCENESSE®. The lack of an available therapy has led to a lack of incentive for patients to seek medical consultation. From a different perspective, physicians have historically seen a delay in the diagnosis of this rare affliction and have not been required to clinically deepen the characterisation of the disease owing to the lack of sufficient patients attending clinics.

PREVALENCE AND KNOWN PATIENT POPULATION IN ENGLAND

As referenced, the prevalence of EPP is estimated to be 1:140,000[1] in Western European countries, with the largest number of patients having been diagnosed in the Netherlands, Germany and England. In England, on the basis of prevalence the total number of EPP patients could theoretically be **513 EPP patients** when accounting for a current UK population of 54,800,000[2].

However, on the basis of empirical clinical data and personal correspondence between CLINUVEL's clinical teams and the expert physicians in England during 2005 to 2016, as explained in detail within this document [redacted]. The 2006 publication of Holme et al. estimated a total number of **389 EPP adult patients in the UK**, excluding four children[3]. [redacted]

During the clinical trials CUV017 (Phase III, cross-over design) and CUV029 (phase III randomised placebo-controlled design), CLINUVEL had enrolled [redacted] **UK EPP patients** in 2009 and 2011 respectively.

For completeness, in Wales there are known to be [redacted] adult EPP patients, while in Scotland there are [redacted] adult patients known to seek treatment.

CLINICAL DILEMMA AND IMPACT OF EPP

EPP patients suffer from a lifelong disorder which is poorly characterised in medical literature and textbooks owing to the lack of a focussed clinical speciality for EPP and cutaneous porphyrias. Porphyrinologists have historically focussed on the group of acute porphyrias and not on the cutaneous porphyrias since no treatment modalities had been available for the latter.

The genetic disorder causes, from birth onwards, a toxicity to photons emitted by light sources, since the excitation of protoporphyrin IX in blood plasma leads to rapid tissue destruction of the endothelium (blood vessels) and hepatobiliary ducts. Clinically, patients suffer from exorbitant internal burns, expressed by lack of better words as "pain". However, this "pain" is unresponsive to analgesics and opioids. It therefore cannot be treated pharmacologically and is inadequately and inappropriately described as "pain". Currently an accurate lexicon is not available to describe the internal ordeal EPP patients are subject to during phototoxic reactions. These reactions manifest as generalised and locoregional oedema, general malaise, ulcerations, and psychological instability and decompensation. The internal ordeal caused by exposure to light sources occurs at dermal and capillary level and is, until the stage of ulcerations, not visible. The invisibility of the disease (the so-called subclinical stage) is an addition frustration for patients who are unable to explain their "pain" and general feeling of illness and this forces patients to withdraw from social and professional life. Most EPP patients start, from the age of infancy, to avoid any light sources and withdraw from a normal active life, which usually leads to a social deprivation of normal human contacts.

Once EPP patients experience the first "burns" they adopt an ingrained anxiety for light and avoid the risk of further exposure. The vicious circle of not wanting to risk exposure is a typical result of the conditioned behaviour developed by EPP patients from infancy and adolescence. At the start of adolescence there is a stage of acceptance and patients develop coping mechanisms to shun light and activities where they are at risk. When career choices are made at the age of adolescence, EPP patients most often have no choice than to forgo opportunities and resort to indoor professions or nocturnal occupations, or do not participate in the workforce at all. Epidemiological studies and longitudinal follow up of professional development in EPP are currently missing. The information available is based on 12 years of interviewing EPP patients.

Another clinical issue in EPP is that of "double jeopardy" caused by the accumulation of protoporphyrin IX. Since tissue accumulation occurs gradually, the storage in the hepatobiliary system leads in 3-5% of EPP patients to terminal liver failure and death. Many patients are lifelong anxious of light exposure and the probability that hepatic failure will befall them. Although EPP patients mask their anxiety remarkably well – and a psychological profile is not yet composed due to the low number of patients – the phenomenon of "double jeopardy" is frequently discussed among patients and influences their daily existence in social isolation.

Differentiating EPP from any other light induced disorder, anaphylactic reactions, and photodermatoses is the phenomenon of the "prodromal phase". EPP patients, when exposed to light sources, are able to discriminate the first signs as afferent nerve stimulation of the exposed dermis. Consequently, the start of anaphylactoid reactions and phototoxic burns compels patients

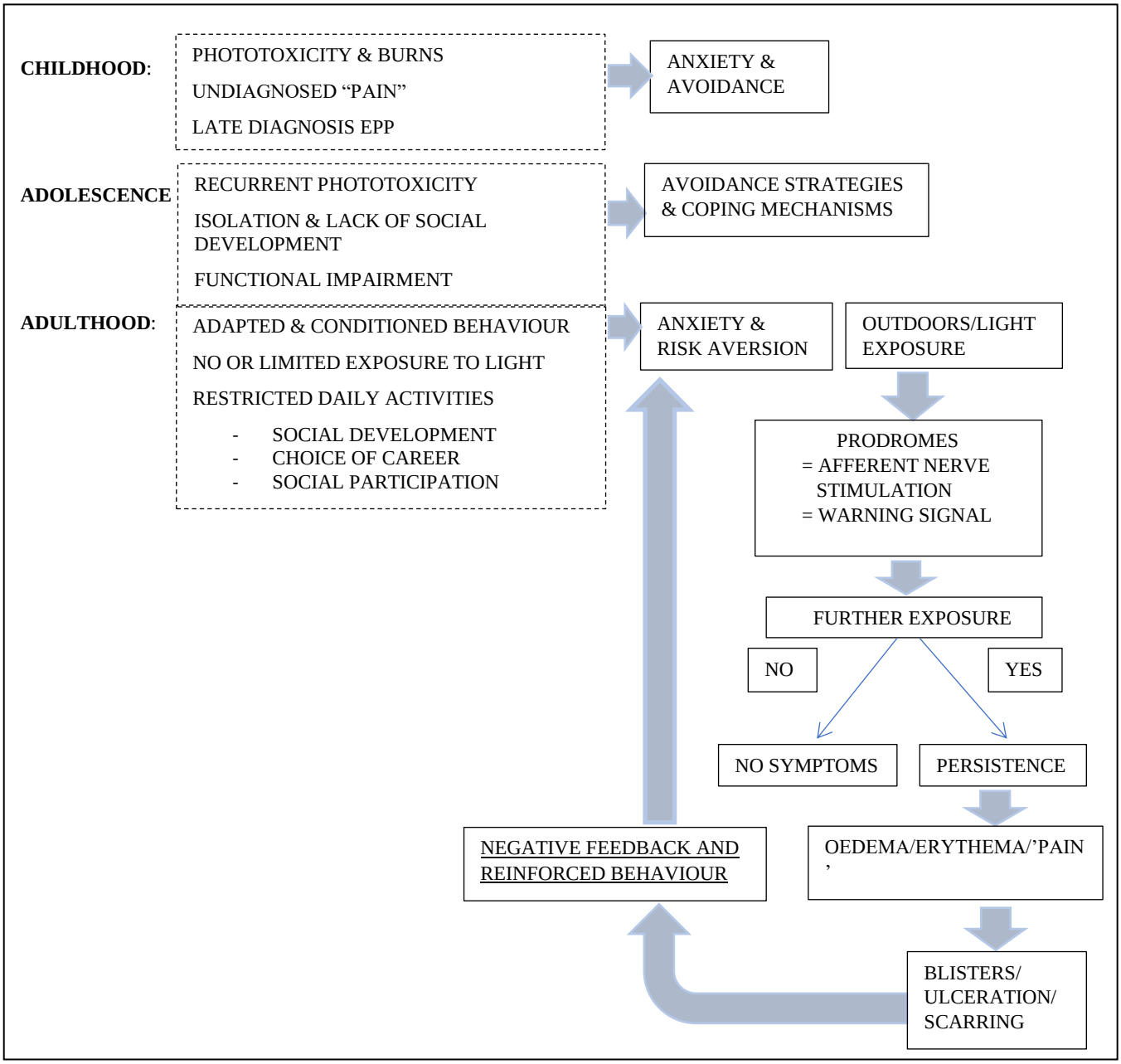
to withdraw immediately from the light and seek shelter. The prodromes often serve as a warning sign for patients to avoid further light exposure. The circle of isolation starts without EPP patients being able to overcome their risk aversion and fear of exposure to daylight and light sources.

In cases where patients are not in the position to avoid light and withdraw, the cascade of phototoxicity starts leading to severe burns of the exposed dermis and surrounding tissues, likened to second degree burns, while the endothelial involvement causes patients an exorbitant ordeal. During these episodes there is demonstrable loss of control by patients and in some cases psychiatric decompensation.

In 1987 Dr Rufener, a psychologist, wrote a PhD thesis on the behavioural aspects of EPP patients. Unfortunately, no further academic attempt has been made to characterise the behaviour of EPP patients.[4]

In **flow diagram 1** the behavioural characteristics of EPP are depicted.

Flow diagram 1. FEEDBACK LOOP ON RISK AVERSION IN EPP PATIENTS



CLINICAL EFFECTIVENESS OF SCENESSE®

SCENESSE® was granted a marketing authorisation (MA) via the centralised approval procedure under exceptional circumstances (in accordance with Article 14(8) of Regulation (EC) No 726/2004). The MA was approved under exceptional circumstances because it was recognised that there are no scientific tools to measure light exposure and the impact of disease. The EMA deemed it therefore necessary to take into account both the overall trend of the clinical data *and the additional evidence of experts and patients diagnosed with a rare condition (including descriptions of individual cases) that was given during the additional expert consultation within the MA approval process*.

The EMA and its rapporteurs acknowledged in all its deliberations in 2014, that EPP was "a complex disorder where the disparity between statistical results and clinical effectiveness was unusually large".[5] The EMA took the position that in the evaluation of SCENESSE® no robust and conventional measure of efficacy would be possible to be developed given the current state of science.

Any further attempt by NICE or its health-economic advisors to use clinical data based on data derived from inappropriate instruments is therefore not only in contradiction to EMA's approval process and marketing authorisation for SCENESSE®, but foremost a desperate attempt to find grounds to argue the effectiveness of the treatment. SCENESSE® is currently prescribed in other European countries where it has been accepted as standard of care for EPP patients.

The health-economic group consulting NICE further use inadequate tools such as the DLQI, and base their scenario analyses to arrive at an expression of impact on quality of life and an invalid QALY score.

The lack of realisation and admission by NICE that poorly characterised disorders such as EPP may have a dramatic impact on patients' lives is amusing, since none of the members of NICE have been exposed to the clinical aspects of EPP. The lack of comprehension by NICE has been consistently expressed since 2015. The latest error of not being able to accept the prevalence data submitted by CLINUVEL and the clinical experts is just one example of the lack of knowledge during the review by NICE. This error alone cost 16 months of delay in the review process, while the appraisal was restarted as if it were a new submission.

The clinical demand for SCENESSE® has been consistent since the first patient had been treated in 2006. Ninety four percent of all EPP patients involved in clinical trials - in total 317 – have requested continuation of the therapy after completion of the clinical trials. In those countries where a compassionate use program, or Special Access Scheme obtained approval SCENESSE® was distributed free of charge for up to two years to patients who had been in clinical trials. In graphical illustration 1, the repetitive use is shown in the years of clinical trials and repetitive use. This number is much higher now since the drug has been used continuously since 2012. [redacted] It is expected that the graphic representation of patients remaining long term on treatment will continue a right shift.

Since market introduction in Europe 98% of the patients requested and received treatment during the second year. [redacted]

[redacted]

The regulatory bodies of Italy and Switzerland first recognised the effectiveness of SCENESSE® and the impossibility to quantify its effect in EPP, and granted the drug a special status in 2010 and 2012, respectively, allowing patients access. The treatment abrogates the anaphylactoid reactions and burns from light exposure.

Since CLINUVEL is the first company globally to have developed a systemic hormonal therapy for the prevention of EPP symptoms, it is not unexpected that adequate scientific instruments to quantify the effect of light emission to EPP patients have been lacking. The absence of scientific research and attention to the disorder led to a void in the development of tools and surveys. This outcome has been recognised by EMA's scientific review, yet dismissed by NICE.

The rationale of the scientific use of afamelanotide in EPP has been provided to national competent authorities in Europe and US, and has been widely accepted. [redacted] The EPP-QOL was used in three EPP clinical trials sponsored by CLINUVEL. [redacted]

In addition, under the current post-marketing surveillance an attempt is made to further measure the effectiveness of SCENESSE® by requesting patients to fill out a survey to qualitatively express the activities patients are able to engage in compared to those prior to treatment.

PROPOSED TREATMENT OF EPP PATIENTS IN ENGLAND

From 12 years of administering SCENESSE® in expert centres during clinical trials and as part of compassionate use programs and Special Access Schemes, [redacted]

SCENESSE® will be made available as a **hospital-only treatment** administered under a multidisciplinary setting and generally at university medical centres and academic hospitals. CLINUVEL will not make the treatment available in general practices or private clinics, nor will SCENESSE® be available to high street pharmacies. **CLINUVEL does not allow for off-label prescription** or administration to any other indication than EPP, as announced consistently publicly. This is a requirement of the Risk Management Plan for SCENESSE® which states that to ensure that SCENESSE® is not used in non-EPP adult patients there must be a controlled access programme to limit the use of SCENESSE® to designated porphyria centres. [redacted]

[redacted]

[redacted]

In **figure 1** the distribution of known expert centres in porphyria, as well possible new centres in England are illustrated. At the time of print, CLINUVEL has only worked with [redacted] The other centres do have expertise [redacted]

By virtue of his clinical excellence and lifelong devotion, the academic expert in two of the most severe light induced disorders, xeroderma pigmentosum and cutaneous porphyrias, [redacted] is the most eminent clinician who has seen the largest number of EPP patients despite the lack of available treatment. [redacted]

In [redacted] the academic expert in photobiology and cutaneous porphyrias is [redacted] has participated in CLINUVEL's sponsored CUV017 (phase III cross-over design) and CUV029 (phase III randomised placebo-controlled design) trials.

During the CUV017 and CUV029 trial, [redacted] EPP patients were enrolled by [redacted], respectively.

In England, there are a number of photobiologists, photodermatologists, hepatologists and geneticists who have provided clinical consultations to EPP patients, without claiming to be experts.

Most global experts in porphyrias are member of the European Porphyria Network (EPNET) and/or the American Porphyria Consortium. [redacted]

[redacted]

[redacted]

[redacted]

TOTAL BUDGET IMPACT SCENESSE® IN ENGLAND

[redacted]

Since the estimated percentage of adult EPP patients is 79%, as per estimations by the Office of National Statistics (ONS), [redacted] When projecting on a theoretical basis a total EPP population of 513 in England, [redacted]

In CLINUVEL's first submission in 2016 the identical numbers and rationale were provided, but were dismissed by NICE without further consideration or diligence. **This omission has cost the Company and more importantly EPP patients an additional 16 months of deprivation of treatment**.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CONDITIONS OF EUROPEAN SUPPLY OF SCENESSE®

CLINUVEL has worked with the global expert centres during 12 years of research and development of SCENESSE®, and has learned how physicians and patients across borders have been communicating and seeking treatment by travelling from afar.

However, the CLINUVEL Board of Directors have declared publicly that CLINUVEL will not provide hospitals, physicians or intermediaries with any rebate or discount. The Company is treating each country and all treating hospitals on an equitable basis.

Similarly, CLINUVEL does not pay any rebates or discounts to any healthcare provider, insurer or national health care system globally and pledges to adhere to this statement. Its financial auditors Grant Thornton Ltd are aware of the principle and transparency, while CLINUVEL's financial accounts have reflected this principle since 2005.

CLINUVEL will not enter a discussion with NICE or NHS England on the topic of discounts, rebates, PAS or CAA discounts since the Company is not providing this in any other country in the world. In this manner, each country is treated equitably and without further bias or favour.

CLINUVEL's aim is set to an example in the industry by providing healthcare providers:

(i) an accurate forecast on probable and possible volumes and financial impact
(ii) the assurance that each country in Europe, Switzerland is treated equitably. CLINUVEL bears the risk of currency fluctuations and is only held to adjust the price of SCENESSE® at the end of the financial year depending on the adjustment of the Consumer Price Index (CPI).

SCENESSE® is being distributed to each European expert centre under passive cold chain transportation, while CLINUVEL bears the transportation cost of the drug.

CLINUVEL does not allow financial malpractice, fraud or the existence of off-balance sheet payments or receipts.

The declarations of uniform pricing and equitable treatment per nation CLINUVEL as a publicly listed company are legally binding and published by the Australian Securities Exchange (ASX) and Deutsche Aktienindex (DAX).

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[redacted]

[redacted]