



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](http://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<sup>1</sup>. 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<sup>1</sup>. 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,

Dr Rocco Falchetto on behalf of IPPN

Co-founder and *a.i.* Chairman of the International Porphyria Patient Network, and Chairman and co-founder 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 <sup>2-4</sup> .
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.	<p>This statement is inaccurate: In the 2015 Biolcati et al. observational study<sup>5</sup>, 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 Porphyrrias 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.<sup>5</sup>, underscores the effectiveness of afamelanotide in improving patient lives.</p> <p>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 imagine 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</p>

		<p>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.”</p> <p>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<sup>1</sup>).</p> <p>From this collective evidence we conclude that the afamelanotide treatment <b>is clearly</b> and significantly effective and of benefit to EPP patients, and do not agree with the committee’s assessment that the treatment <b>may be</b> effective and that it is <b>unclear</b> how effective it is.</p>
<p>1.2(c), 4.10, 4.14</p>	<p>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.</p> <p>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.</p>	<p>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:</p> <ol style="list-style-type: none"> <li>1. At least 2 of the 10 questions of the DLQI do not apply to EPP (Q 9&amp;10), which reduces responsiveness/sensitivity.</li> <li>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.</li> <li>3. The responsiveness/sensitivity of the DLQI has never been validated for the efficacy assessment of a treatment for EPP.</li> </ol> <p>The limitations of health status (HS) scores have been elaborated by Hamming &amp; De Vries<sup>6</sup>: They highlight that the World Health Organisation (WHO) working group has defined QoL as “the concept with emphasis on the <u>personal evaluation</u> of functioning in relation to individual and/or cultural standards, values, expectations and goals<sup>7</sup>”. Therefore, the perception of disease and treatment should not only be <u>recorded</u> (e.g., by measuring HS scores), but also <u>evaluated</u> by the patient, as Hamming &amp; 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<sup>6</sup>.” 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.<sup>5</sup> 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 &amp; De Vries<sup>6</sup>. 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.<sup>5</sup>). 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 <b>4.0 ± 2.9 and 8.0 ± 1.9, respectively, with the difference having a statistically high significance (P &lt; 0.001)</b> (Biolcati et al.<sup>5</sup>). This direct evaluation of</p>

	<p>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.</p>	<p>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.</p> <p>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]<sup>8</sup>), nor real world evidence such as that reported by Biolcati et al.<sup>5</sup>. 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<sup>1</sup>), 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<sup>1</sup>).</p> <p>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)<sup>9</sup>, after which a pricing agreement was reached and a reimbursement amount binding for all German state health insurers was set<sup>10</sup>. 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.</p>
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 <sup>11</sup> , 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.	<p>This is inaccurate since Holme et al.<sup>12</sup> 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).</p> <p>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.</p>
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.	<p>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<sup>5</sup>, 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.</p> <p>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.</p>
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 <sup>5</sup> , 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. <sup>5</sup> 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.	<p><u>This is a key issue:</u> 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.</p> <p>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<sup>1</sup>) has to be considered as a substantial improvement.</p>
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.	<p>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.<sup>5</sup> 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.</p> <p>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<sup>1</sup>)."</p> <p>Here, it is important to refer once more to Hamming &amp; De Vries<sup>6</sup> 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 23<sup>rd</sup> 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</p>



		<p>without amendment or interpretation of the patient's response by a clinician or anyone else<sup>13</sup>." 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<sup>1</sup>)."</p>
4.9(b)	<p>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.</p>	<p>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<sup>5</sup> and who used patient input to appropriately formulate the questions.</p> <p>Second, the modification of the questionnaire "while data were being collected" is not relevant because as demonstrated by Biolcati et al.<sup>5</sup> 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<sup>5</sup>."</p> <p>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<sup>1</sup>)." 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.</p>
4.9(c)	<p>The committee concluded that the EPP-QoL did not appear to capture aspects of EPP that</p>	<p>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</p>

	<p>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.</p>	<p>this, in addition to those used in the Biolcati et al. paper<sup>5</sup>. 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.</p> <p>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<sup>14</sup>.” 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. <u>Not doing so is a discrimination against EPP patients which we find extremely concerning.</u> 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.</p>
4.11	<p>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.</p>	<p>See our comments to section 4.9</p>
4.3, 4.20	<p>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.</p> <p>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</p>	<p>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.</p> <p>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<sup>1</sup>), 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.</p> <p>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</p>

	<p>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.</p>	<p>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.</p>
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## References

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