6 June 2018

Dr Rosie Benneyworth
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10 Spring Gardens
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Dear Dr Benneyworth

Re: Final Evaluation Determination – Afamelanotide for treating erythropoietic protoporphyria (ID927)

The International Porphyria Patient Network (IPPN) would like to appeal against the Final Evaluation Determination for the above mentioned highly specialised technology on the following grounds:

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

a) failed to act fairly

or

b) exceeded its powers

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

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

1a.1 The committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit

Patient representatives at the NICE committee meetings and all 14 comments submitted during the consultation phase by individual patients with treatment experience state massive treatment effects, i.e. that under treatment they are able to stay for hours in sunlight and have an almost normal life (committee papers p.37-68). On the one hand the committee listed the benefits in its Final Evaluation Document (hereafter FED): *"The committee took into consideration patient reports that afamelanotide resulted in much better outcomes than it had in the clinical trials. For example, a patient expert at the meeting stated that afamelanotide had allowed him to increase the time he spent in light by hours rather than by minutes (as had been seen in the trials) and described this as life changing. One clinical expert stated that the response of the patient expert to afamelanotide was similar to the anecdotal evidence he had heard from other people who had received afamelanotide. There was strong feedback from the experts that afamelanotide is a highly effective treatment option for a poorly characterised and debilitating condition. The comments from individual patients received during consultation reiterated these testimonies"* (FED p. 10). On the other hand the committee maintained its interpretation that the benefit of the treatment is small, despite the real world evidence on a significantly positive treatment effect. The committee concluded that *"Clinical trial results suggest small benefits with afamelanotide"* (FED p.1), and that *"overall, afamelanotide does not appear to provide value for money within the context of a highly specialised service, and cannot be recommended for routine funding in the NHS"* (FED p.2).

Despite the positive patient testimonies, the committee still maintained their preliminary recommendation and interpretation that the benefit of the treatment is small, i.e. a few minutes in sunlight and that the efficacy is not accurately quantifiable and the extent of the benefit uncertain.

Thereby the committee is (a) effectively overriding the evidence provided by patient testimonies and expert physicians on the clinical benefit and (b) not adequately responding to the scientific arguments put forward in the statements submitted by the consultees, such as IPPN, on why the measured efficacy does not represent a small benefit but a reasonable improvement (see point 2.1 and 2.2 in this document). IPPN rejects the interpretation of the trial results as representing a small benefit simply because the true benefit is not accurately quantifiable. IPPN demands that the real world evidence provided by patients and expert physicians be appropriately taken into consideration otherwise the consultation process would be reduced to a futile exercise without real meaning and the decision to access a life-changing treatment would be solely based on individual opinions of committee members instead of a scientific, transparent and fair decision making process (see points 1a.2 and 1b.1).

1a.2 The committee failed to act fairly by omitting to discuss the evidence and the arguments provided by the consultees in a scientific and transparent way

In general, the impression is created that the evaluation by NICE is not sufficiently based on scientific principles: Instead of a scientific discussion of the evidence presented by the expert physicians and patients, throughout the evaluation documents NICE simply stated that an argument put forward *"has been considered"*, *"was noted"* or that the committee *"was aware of"* it. However, as the evidence is not reflected in the conclusions of the committee, the conclusion of the committee is not valid (examples below).

1a.3 The committee failed to act fairly by choosing an approach for its assessment which knowingly underestimates the benefit of the treatment and therefore actively discriminates against EPP patients

The committee admits that it has knowingly chosen an approach to evaluate the cost/benefit ratio of afamelanotide which underrepresents the real benefit: "*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*" (FED p.16). From the FED document we understand that treatments compete with each other for funding (a rationing approach which we by itself consider ethically highly questionable): "*The committee was aware of the importance of the consistent approach used by NICE and the NHS to ensure fair allocation of finite budgets because funding of a treatment may mean other treatments or services are displaced*" (FED p.14). As a consequence, the underrepresentation of the benefit by the approach chosen to evaluate the afamelanotide treatment results in a systematic and undue discrimination of EPP patients compared to other, more appropriately evaluated applications for reimbursement.

In public presentations detailing the HST evaluation process, NICE representatives acknowledge the limitations of trial design and generation of efficacy data in small populations and emphasize the importance of patient input, e.g. that *"limited evidence base means patient evidence is particularly important for HST evaluations"* (presentation by Sheela Upadhyaya; January 2015). In the light of the acknowledged underrepresentation of the benefit of the afamelanotide treatment in the clinical trial outcomes, we urge the committee to take patient testimonies on the real benefit of the treatment into account, i.e., that the effect of the treatment is not a few minutes but in the range of hours of additional pain-free sunlight exposure and has a transformative effect on patients' life and that of their families.

Reference:

http://www.findacure.org.uk/wp-content/uploads/2016/02/Sheela-Upadhyaya-slides.pdf (Last accessed 2 June 2018)

1a.4 The committee failed to act fairly by denying a Managed Access Agreement (MMA) based on the same arguments put forward on why it already rejected a recommendation for reimbursement, thereby using circular reasoning which leaves no possibility for access whatsoever

The committee concluded that because of the complexity and rarity of the condition and lack of sufficient tools, the efficacy cannot be accurately quantified in EPP and assumes that the true benefit is likely underrepresented in the trial data. The uncertainty in the extent of the benefit is stated as the reason for why afamelanotide cannot be recommended for reimbursement. However, a MAA in which further data is collected in patients receiving the treatment is also not supported, out of the same reasons: "*The committee accepted that data collection in the context of a MAA was unlikely to resolve the existing uncertainties in the evidence base because it was likely to face challenges similar to those faced in the trials*" (FED p.21). Thus the committee in other words accepts itself the limits of clinical trials / real-world-data-gathering with regard to the proof of afamelanotide's therapeutic value. Consequently, the committee would have had to propose other means of evaluation instead of at the same time acknowledging evaluation-limits of standard evaluation-means but not judging accordingly. The committee acted as if 50 children in too hot a bath cried for being burnt, but because the thermometer is not working, the obvious truth is neglected. The formalistic approach of the committee does not do justice to the need of a humanitarian interpretation of the obvious.

Holme et al. 2006 measured the blood concentration of the phototoxic metabolite "protoporphyrin" in the British EPP cohort and determined a 78-fold difference between the lowest and highest concentration of protoporphyrin, which makes EPP an extremely heterogeneous condition. In addition, EPP symptoms are

triggered by sunlight, but also artificial light, light reflected from bright surfaces and snow, and are exacerbated by many factors like cold wind and heat (Holme et al. 2006). However, the exact composition of factors which trigger the phototoxic reactions are unknown, they cannot be accurately quantified and standardised. Because of the rarity and complexity, uniqueness and incomplete understanding of the condition, an accurate quantification of the treatment effects is therefore not possible and presumably will not become possible in the near future. Despite those limitations, significant efficacy outcomes were measured in three phase III trials and in the larger of the phase II clinical trials, collectively comprised of 350 patients (European Public Assessment Report of afamelanotide, hereafter EPAR, p. 74-75) and a substantial and lasting increase in quality of life could be demonstrated for 115 patients (Biolcati et al. 2015) in a long-term observational study. Not acknowledging these achievements in such a complex and unique condition as EPP would be an extremely unfair act against EPP sufferers compared to conditions with affect more people, have a longer research history and in which previous experience exists on how to develop treatments and measure their effects.

References:

European Public Assessment Report (EPAR) of afamelanotide, 23 October 2014; EMA/CHMP/709396/2014 Rev.1
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002548/WC500182309.pdf.

Biolcati, G., Marchesini, E., Sorge, F., Barbieri, L., Schneider-Yin, X., & Minder, E. I. (2015). Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. British Journal of Dermatology, 172(6), 1601-1612.

Holme SA, Anstey AV, Finlay AY et al. Erythropoietic protoporphyria in the UK: clinical features and effect on quality of life. Brit J Dermatol 2006; 155: 574-81

1a.5 The committee failed to act fairly by not ensuring full representation of the patients' voice at the committee meetings

For the meeting in February 2018 IPPN nominated a patient representative who works in research and diagnostics of porphyrias and has long-term (> 5 years)

experience in the afamelanotide treatment herself. IPPN pointed out in exchanges with NICE officials that, unlike in other countries with access to afamelanotide, no patient representative with long-term experience with the treatment exists in the U.K. and that therefore national patient representatives cannot cover this specific and in the context of EPP very important aspect. Nonetheless, NICE still declined to include IPPN's candidate as patient representative at the February meeting. In addition, of the two British patient representatives invited to participate in this committee meeting only one attended in the end, leading to a regrettable and further underrepresentation of the patient perspective.

1a.6 The committee failed to act fairly by demonstrating a consistent discrimination against IPPN as a stakeholder group

IPPN was involved in the process of the HST workshop held on 23 March 2016 to discuss afamelanotide in the treatment of adult EPP patients, with two British patients attending on behalf of IPPN. However, for reasons unknown to us and not clarified by NICE, IPPN was then not invited to the 23 November 2017 committee meeting. It should have been NICE's responsibility to reach out to IPPN for further inclusion in the process. Instead, after belatedly learning about the ongoing process, IPPN had to proactively reach out to NICE to ensure that they be included as formal consultees, which was initially denied out of reasons which turned out to be incorrect: administrator for Technology Appraisals & HST at NICE, stated that (1) NICE was unable to add IPPN to the stakeholder list because IPPN is an international organization, and (2) that it would be too late in the process to add IPPN to the stakeholder list (E-mail to Dr. Rocco Falchetto, President of IPPN on January 6th 2018). However, there is no indication whatsoever on NICE's guidance documents that international organizations are not allowed in the process and examples exists of instances where international patient organizations are or have been consultees in a technology evaluation process (e.g., in the appraisal process of Elosulfase alfa for treating mucopolysaccharidosis type IVA and Avelumab for treating metastatic merkel cell carcinoma).

After putting forward the above mentioned arguments, IPPN was finally accepted as a consultee and provided a formal statement. However, IPPN representatives were still not allowed to participate in the February 2018 committee meeting (see also point 1a.5) and were therefore denied the opportunity to provide input in an interactive way by directly answering questions or clarifying aspects related to their statement and reacting to new elements raised by the committee during the discussion. The IPPN representative who applied to participate in the meeting, Dr. Jasmin Barman-Aksözen, is in the unique position of being a specialist in the field of porphyrias herself, having long-term experience with the treatment, having been a patient representative during the approval process of afamelanotide at the European Medicines Agency (EMA) and having been involved in the German Health Technology Assessment process. The document "Highly Specialised Technologies: a factsheet for patient and carer organisations" provided to IPPN by , NICE, on February 8th 2018, explicitly recommends to nominate *"1. A patient expert with a broad knowledge of the condition, current treatments, new treatment and outcomes that are important to patients, 2. A patient expert with personal experience of the condition, and where possible the treatment under evaluation."* British patients do not have access to the afamelanotide treatment, however from the experience gained in trials and long-term observations, the anxiety of patients to be exposed to light have to be overcome by the patients in order to appreciate the full benefit of the treatment, a process which might take several years. EPP is an ultra-rare, unique and poorly understood condition, with a limited number of people able to provide this level of expertise, and discriminating against IPPN by preventing a full participation of IPPN expert patients deprives the suffers in the U.K. of this crucial support.

In addition, despite being a formal consultee IPPN was not able to be exposed to several other aspects of the evaluation like the discussion surrounding the proxy condition and the DALY, QALY and ICER evaluations which so remain completely unclear and non-transparent, making it impossible for IPPN to give an informed statement on these crucial aspects of the decision-making process. Moreover, the arguments put forward in the statement provided by IPPN were not

considered and no explanation for not taking them into account is provided in the FED. As most of the content of the statement which was not considered concerns evidence, the details are discussed under point 2.

Taken together, there is reason to believe in a systematic discrimination against IPPN, which is an unfounded and unfair action against IPPN and British EPP sufferers, an unequal treatment against other stakeholders which were involved in the entire process and an inacceptable limitation for such an ultra-rare and poorly characterized condition such as EPP.

We urge the committee to ensure that IPPN be fully included in any future discussions on afamelanotide and invited to provide their input not only in writing but also in person by proactively enabling their full participation in any meetings related to this matter going forward and granting them the same rights and opportunities as the other stakeholders.

Reference:

Guidance document (point 6 and 7):

https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf

1a.7 The committee failed to act fairly by not declaring a potential conflict of interest of a lead committee member

member of the lead team of the afamelanotide evaluation in the committee, is Vice-President for Market Access at Biogen Idec, a company which *"develops, markets and manufactures therapies for people living with serious neurological, autoimmune and rare diseases"* (https://www.biogen.com/). Currently, afamelanotide is actively investigated for treatment of multiple sclerosis and other inflammatory and autoimmune diseases (Mykicki et al. 2016, Biolcati et a. 2014), and the strong anti-inflammatory and anti-oxidant properties of afamelanotide were known to the committee (FED p.2 and IPPN statement, committee papers p.27). Therefore, a conflict of interest by cannot be excluded, however none was stated by the committee member. As is in

the lead team of the committee preparing the recommendation for afamelanotide, a conflict of interest potentially compromises the decision made by the HST committee.

References:

Highly Specialised Technologies Evaluation Committee members: https://www.nice.org.uk/get-involved/meetings-in-public/highly-specialised-technologies-evaluation-committee/members (Last accessed 2 June 2018)

https://www.biogen-international.com/ (Last accessed 3 June 2018)

Mykicki, Nadine, et al. "Melanocortin-1 receptor activation is neuroprotective in mouse models of neuroinflammatory disease." Science translational medicine 8.362 (2016): 362ra146-362ra146.

Biolcati, G., et al. "Efficacy of the melanocortin analogue Nle4-D-Phe7-α-melanocyte-stimulating hormone in the treatment of patients with Hailey–Hailey disease." Clinical and experimental dermatology 39.2 (2014): 168-175.)

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

1b.1 The committee exceeded its powers by basing its decision on opinion rather than on evidence

The committee concluded that "*Clinical trial results suggest small benefits with afamelanotide. Testimonies from patients and clinical experts suggest that the benefits may be greater than those seen in trials, and that even small improvements would be of great importance to them. The true benefit of afamelanotide has, however, not been quantified*" (FED p. 1). IPPN rejects the interpretation of the trial results as representing a small benefit simply because the true benefit is not accurately quantifiable (see 1a.1) and, as no rationale is presented by the committee on why the benefit of the treatment should be small, it cannot be excluded that the assessment was based solely on the opinion of the committee members. In order to make an informed and evidence based decision, the committee needs to use all the evidence available. In rare diseases, patients,

their caregivers and specialised physicians are better positioned to comment on benefit than a committee or EGR which might have never even met a patient. In case there is uncertainty on the extent of the benefit, patients with long-term treatment experience are the best individuals to comment on real life benefit – or lack thereof – of a treatment. By overriding the patients' inputs NICE exceeded its powers because it is ignoring the evidence provided by the group of stakeholders with the most direct, experiential insights.

1b.2 The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward

One of the questions for consultation was if there are *"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 responded in its statement by explaining that EPP patients only have this one approved and effective therapy available and that by not recommending its reimbursement, *"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"* (Committee papers p. 24). As an answer, the committee in the "Response" column in the Committee papers (p.24) simply stated that "*No potential equalities issues have been identified*", without providing further evidence for their assessment. Without evidence however, the committee is deciding arbitrarily and therefore potentially misuses its power, dismissing opposing arguments without giving any plausible counter-arguments.

1b.3 The committee exceeded its powers by re-assessing the regulatory conclusions of the European Medicines Agency

Instead of building on the regulatory approval granted by the European Medicines Agency (EMA), as it would be expected in any national health technology assessment process, and despite IPPN's numerous reminders and references to the conclusions of EMA, NICE has repeatedly exhumed questions which had already been addressed during the regulatory approval process, and re-assessed EMA's conclusions without providing any reasons. In fact, by not recommending afamelanotide for reimbursement by the NHS because the real benefit is not quantifiable NICE makes an absolute mockery of EMA's regulatory approval under exceptional circumstances: *"Directive 2001/83/EC, as amended, Annex I, Part II, documentation for applications in exceptional circumstances, states that when, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:*

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

- In the present state of scientific knowledge, comprehensive information cannot be provided, or

- It would be contrary to generally accepted principles of medical ethics to collect such information,

a marketing authorisation may be granted subject to certain specific obligations."

We express our utmost concern for the abuse of power displayed by NICE in the evaluation of afamelanotide for treating EPP, which de facto ignores the overriding authority of EMA, calls into question the entire regulatory approval process, and prevents British EPP sufferers from accessing a life-changing technology, discriminating against them compared to other EPP patients in Europe.

References:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf (Last accessed 2 June 2018)

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

2.1 The evidence provided shows that the benefit is significant and not small, as assessed by the committee

All patient representatives at meetings and all comments from individual patients with treatment experience state a transformative effect of the afamelanotide treatment: The treatment enables patients to be outside in sunlight for hours and to lead an almost normal life. The statements of the patients are supported by expert physicians, and the long-term observational study in 115 Swiss and Italian EPP patients in compassionate use and extended access programmes (Biolcati et al. 2015): Quality of life increased from initially 32 % to 74% of the maximum possible, and patients showed an overwhelming treatment adherence with only three out of 115 patients stating lack of efficacy as reason to discontinue the therapy. In all four clinical trials, significant treatment effects were measured despite the many limitations in trial design and complexity and incomplete understanding of the condition. The committee acknowledged the benefit the treatment provides, however arbitrarily and in contrast to all other evidence provided chose to rate its extent as small: "*The committee agreed that afamelanotide was effective and that the true benefit had not been quantified*" (FED p.22).

Reference:

Biolcati, G., Marchesini, E., Sorge, F., Barbieri, L., Schneider-Yin, X., & Minder, E. I. (2015). Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. British Journal of Dermatology, 172(6), 1601-1612.

2.2 The evidence provided of the measured trial outcome shows that the treatment is highly effective

IPPN strongly objects to the interpretation of the committee that the efficacy is small only because it is not accurately quantifiable and maintains that the measured trial outcomes show that the treatment is highly effective. In its statement IPPN put forward two crucial arguments on how the trial results have to be interpreted. Regrettably and inexplicably, both arguments were ignored in the final evaluation:

(a) In the FED the committee reiterated the dichotomy between the patients' experience under treatment with afamelanotide, which has enabled them to expose themselves to sunlight for hours and to experience a life-changing effect, and the trial outcomes which seem to indicate only a few minutes extra sunlight per day. IPPN put forward the argument that the trial outcome is a calculated average value, standardised to minutes per day, but that this standardisation does not consider that the trial period included rainy days and working hours (Committee papers p.32). The patients on the other hand refer to individual days on which they had the time to be outside. In the trials, spontaneous light exposure under quotidian conditions was quantified, and not the maximum possible time patients under treatment are able to expose themselves to sunlight, i.e., light tolerance. Patients exposing themselves on a distinct occasion, like a weekend trip with the family, experience the real full efficacy that the treatment provides for them, i.e., their new limits in light tolerance which can make a difference between a few minutes until the first phototoxic reactions without treatment to several hours under therapy. This effect is described by the patients as transformative and has far reaching positive effects on their entire life.

(b) The second argument put forward by IPPN concerns the extent of the benefit. The committee judged that the *"few minutes"* (average 10.8 additional minutes as calculated from the original CUV039 trials results) per day an EPP patient under therapy can spend in sunlight "suggests small benefits" (FED p.1). However, in

order to objectively evaluate the additional time EPP patients can expose to sunlight as measured in the clinical trials, this time has to be compared to the time normal people spend outdoors on average. In its statement IPPN put forward the argument that while the average daily time of sunlight exposure of a normal population in UK is unknown, one can estimate it from the widespread vitamin D deficiency in a normal population: Vitamin D deficiency could be alleviated by only 15 min sunlight exposure per day, therefore it can be extrapolated that the daily average spontaneous sunlight exposure in a normal U.K. population ranges in the minutes and certainly not hours (Committee papers p.32). Meanwhile, IPPN performed an extensive literature search on the daily time normal people spend in sunlight / outdoors. In the identified five studies, the measured lower limits range between one to 18 minutes outdoors per day. This comparison shows that EPP patients under treatment reach and even exceed the average lower limits normal people expose themselves to sunlight and that the afamelanotide trial outcomes therefore should not be assessed as being small.

References:

Diffey, B. L., & Norridge, Z. (2009). Reported sun exposure, attitudes to sun protection and perceptions of skin cancer risk: a survey of visitors to Cancer Research UK's SunSmart campaign website. British journal of dermatology, 160(6), 1292-1298.

Graham, S. E., & McCurdy, T. (2004). Developing meaningful cohorts for human exposure models. Journal of Exposure Science and Environmental Epidemiology, 14(1), 23.

Isaacs, K., McCurdy, T., Glen, G., Nysewander, M., Errickson, A., Forbes, S., ... & Vallero, D. (2013). Statistical properties of longitudinal time-activity data for use in human exposure modeling. Journal of Exposure Science and Environmental Epidemiology, 23(3), 328.

McCurdy, T., & Graham, S. E. (2003). Using human activity data in exposure models: analysis of discriminating factors. Journal of Exposure Science and Environmental Epidemiology, 13(4), 294.

Thieden, E., Philipsen, P. A., Heydenreich, J., & Wulf, H. C. (2009). Vitamin D level in summer and winter related to measured UVR exposure and behavior. Photochemistry and photobiology, 85(6), 1480-1484.

2.3 The evidence provided shows that quality of life before treatment is low and under treatment with afamelanotide increases dramatically and sustainably

In the eight-year observational study by Biolcati et al. (2015) in 115 Swiss and Italian EPP patients in compassionate use and special access programs, quality of life was measured with the disease specific questionnaire "EPP-QoL". During this study quality of life increased from 32 % at baseline to 74 % under treatment and remained high throughout the entire study period. Nonetheless, "*the committee concluded that afamelanotide was likely to improve quality of life but the true size of any improvement was uncertain*" (FED p.10). In addition, the committee chooses not to base their evaluation on the disease specific instrument EPP-QoL but on the generic instrument DLQI, although the DLQI in the opinion of the patients and expert physicians neither adequately reflects the condition nor the treatment effects but knowingly leads to an underrepresentation of the benefit. There are multiple reasons for why we do not agree with the committee's decision to use the DLQI and maintain that data from the more appropriate EPP-QoL should have been used instead:

(a) The disease specific quality of life instrument "EPP-QoL" is the more appropriate tool to measure quality of life in EPP: It was developed together with expert physicians and is partly validated for the condition, while the generic instrument "DLQI" is only validated for other conditions but not for EPP. As put forward by IPPN in its statement, the European Medicines Agency in its Guidelines for Trial design in Small Populations recommends using disease specific quality of life instruments, even if the patient population is too small to perform a full validation (Committee papers p.34). In addition, patients and physicians rate the DLQI as not appropriate: *"The committee heard from the patient experts that the DLQI includes questions that are not relevant to EPP, such as feelings of embarrassment or self-consciousness relating to skin conditions, and that it does not capture non-skin components of EPP such as fatigue. The committee further heard from the clinical experts that the DLQI does not ask anything about exposure to light, unlike the EPP-QoL"* (FED p.12).

(b) The EPP-QoL has been shown to be sensitive to measure treatment effects and even detects differences in quality of life between summer and winter seasons (Biolcati et al. 2015), while the DLQI has been shown not to be sensitive to treatment effects: *"The committee noted that DLQI data from the trials had shown a modest but not statistically significant improvement in quality of life with afamelanotide …"* (FED p.23). The committee nevertheless chose to base its cost/benefit calculation on the data obtained with the DLQI, although it was well aware of the fact that this approach underestimates the real benefit: "*However, it reiterated questions about whether the DLQI measured in the trials adequately captured the quality of life associated with EPP and the benefits of afamelanotide (see section 4.11). 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*" (FED p.16)

(c) The arguments put forward by the committee on why it preferred the DLQI seem to be based on two unrealistic expectations: *"The committee heard that, in the long-term observational study (Biolcati et al., 2015), quality-of-life scores measured by the EPP-QoL (a condition-specific quality-of-life questionnaire) increased from 32% to 74% of the maximum in the first 6 months of treatment with afamelanotide, with little change over the next 6 years of observation. This indicated that there was no marked improvement in the quality of life of patients who had treatment beyond the duration of the controlled clinical trials. […] The committee considered that these results were in contrast to the discussions around the impact of conditioned light avoidance"* (FED p.9-10). This statement is difficult to understand: Either the committee mistakenly interprets that quality of life increased from 32% to 74% and then decreased again, which would obviously be incorrect (quality of life increases to 74% and remains at that level without decreasing). Or the committee thinks that while the demonstrably insensitive, non-validated DLQI instrument is used for quantification of the benefit of the afamelanotide treatment, a significant and consistent long-term increase in quality

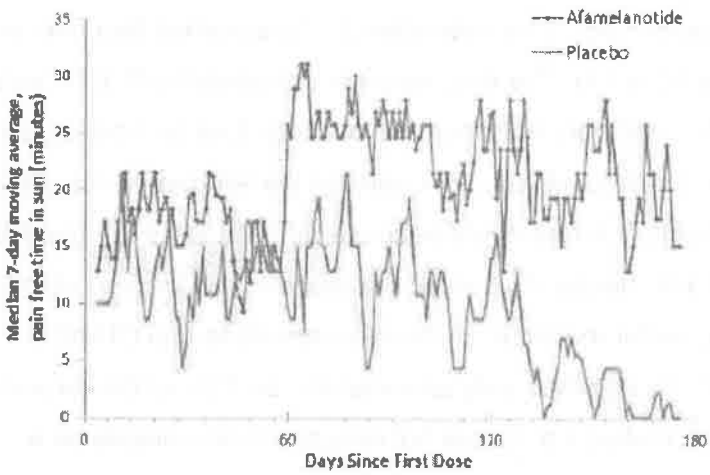
of life measured by the partly validated disease specific instrument is not sufficient because the quality of life does not increase above 74% after the first 6 months of treatment. In its statement IPPN put forward the argument that an increase over 80% cannot be expected (Committee papers p. 31). In addition, below we provide evidence from the approval process which EMA interpreted as the overcoming of the conditioned light avoidance behaviour (box 1):

Box 1: Evidence for overcoming of conditioned light avoidance behaviour after experience with the treatment

In the figure below, depicted from the public documentation of the approval process of afamelanotide (EPAR p.71), longitudinal pain free time in sunlight as measured in the CUV039 trial is shown for the treatment (blue) and placebo group (orange). Values are expressed as median of 7 days pain free time in sunlight (minutes). While in the first 60 days, no major difference is visible between afamelanotide and placebo, the two groups do show significant and consistent differences in their sun exposure behaviour for the rest of the study period, i.e., the following 120 days. The figure shows that patients only increase their exposure to sunlight with the second treatment dose. The measured difference between the two groups has in our opinion two reasons: a) the full treatment effect is only achieved after the second dose and b) patients needed time to adapt to the new limits in sun exposure by, amongst other things, overcoming both their anxiety and learned sun avoidance behaviour.

Figure 06 (figure 11.1 as named by the Applicant)

Figure 11.1 Longitudinal trends in direct sunlight exposure (ITT population, Diary Card)



The Applicant concludes from these results that there is a consistent difference in pain-free direct sunlight exposure between the treatment groups and that the differences between the treatment groups in the longitudinal patterns support the hypothesis that subjects treated with afamelanotide are better able to tolerate direct sunlight exposure and overcome the anxiety previously associated with such exposure.

(d) The arguments put forward by the committee on why it preferred the DLQI are not scientifically valid: The committee argues that "*…in a large observational study, it [the DLQI] had been shown to be sensitive to the impact of EPP on people with the condition*" (FED p.13). However, as put forward by Dr Lesley Rhodes at the committee meeting on 20 February 2018, the referred study by Holme et al. (2006) was conducted before an effective treatment existed and therefore it is not clear from this study if the questionnaire is sensitive to treatment effects. Moreover, causality was not established: Holme et al. observed a week positive correlation (Spearman rank correlation =0.228; p=0.002) between blood protoporphyrin concentration and lower quality of life in adults. The causal relationship was however not established, and the lower quality of life demonstrated by the DLQI could be caused by a variety of different reasons like more childhood trauma in patients with higher protoporphyrin concentrations or more liver damage. Therefore, the positive correlation between protoporphyrin concentration and lower quality of life found by Holme et al. does not

automatically qualify the DLQI to be an instrument suitable to determine treatment effects. Another reason put forward by the committee on why the DLQI is preferable over the EPP-QoL is that the EPP-QoL does not contain questions on whether pain was experienced: "*The committee [...] maintained that pain was an important outcome*" (FED p.11). The extreme pain associated with EPP indeed is a unique feature of the condition; however, we consider it as an inadequate outcome measure for the determination of quality of life improvements: Extreme pain in adult EPP patients is a rare event because adult patients adopt a light avoidance behaviour and, hence, do not allow themselves to incur in situations which would result in painful reactions. In the afamelanotide trial CUV039 (Langendonk et al. 2015), pain was only experienced on 12% of the days during the study period, which makes it a severe but rare event not suitable as a sensitive outcome measure.

References:

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Conclusion

In summary, the treatment is demonstrably highly effective (2.1,2.2) and it has a substantial clinical value as both the time to phototoxic events and severity thereof are significantly reduced, the safety and tolerability profile is exceptionally good, and treatment adherence unprecedentedly high. The treatment also shows a pronounced and sustained increase in quality of life (2.3), creating a substantial patient value by reducing both physical and emotional pain and increasing functionality in family, social

and occupational activities. And finally, the societal value that the treatment provides is of high relevance both in terms of reduction of productivity loss, of equity towards a disadvantaged patient population with a hitherto completely unmet medical need and of innovation, being the treatment the first ever to effectively address EPP patient needs.

However, contrary to the evidence submitted to NICE by IPPN and other stakeholders the committee has regrettably given a negative recommendation, which we consider highly unreasonable, also by NICE's own standards: NICE state on their homepage that they work on the basis of the best available evidence: "We use the best available evidence to develop recommendations" (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance). A fair process based on scientific principles and evidence takes into account all the evidence provided. This is particularly important in the case of highly specialised technologies and rare diseases. In the case of afamelanotide and EPP, evidence provided was negligently omitted and carelessly ignored, and the impression is created that many decisions are based on opinions of the committee members instead of the evidence provided, leading to an unfair and unjustified discrimination against a small group of severely affected patients without any treatment alternative. We therefore urge the committee to take our concerns seriously and to revisit their final recommendation by applying appraisal measures in line with the standards NICE publicly proclaim and the considerable evidence presented in support of the significant clinical, patient and societal value of the afamelanotide treatment.

We are requesting our appeal to proceed at an oral appeal.

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